Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1653hxp
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Sep 29	The Philippines Inventory of Chemicals and Chemical Substances (PICCS) has been added to CHEMLIST
NEWS 3	Oct 27	New Extraction Code PAX now available in Derwent Files
NEWS 4	Oct 27	SET ABBREVIATIONS and SET PLURALS extended in Derwent World Patents Index files
NEWS 5	Oct 27	Patent Assignee Code Dictionary now available in Derwent Patent Files
NEWS 6	Oct 27	Plasdoc Key Serials Dictionary and Echoing added to Derwent Subscriber Files WPIDS and WPIX
NEWS 7	Nov 29	Derwent announces further increase in updates for DWPI
NEWS 8	Dec 5	French Multi-Disciplinary Database PASCAL Now on STN
NEWS 9	Dec 5	Trademarks on STN - New DEMAS and EUMAS Files
NEWS 10	Dec 15	2001 STN Pricing
NEWS 11	Dec 17	Merged CEABA-VTB for chemical engineering and biotechnology
NEWS 12	Dec 17	Corrosion Abstracts on STN
NEWS 13	Dec 17	SYNTHLINE from Prous Science now available on STN
NEWS 14	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS 15	Jan 05	AIDSLINE is being removed from STN
NEWS 16	Feb 06	Engineering Information Encompass files have new names
NEWS 17	Feb 16	TOXLINE no longer being updated

NEWS EXPRESS	FREE UPGRADE 5.0e FOR STN EXPRESS 5.0 WITH DISCOVER! (WINDOWS) NOW AVAILABLE
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:36:05 ON 29 MAR 2001

=> file medline, biosis, biotechds, biotechabs, scisearch, dgene, embase, uspat, wpids, hcaplus, japio, fsta, jicst, frosti, cen, ceaba, ca, biobusiness

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.30	0.30

FILE 'MEDLINE' ENTERED AT 10:37:06 ON 29 MAR 2001

FILE 'BIOSIS' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 BIOSIS(R)

FILE 'BIOTECHDS' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'BIOTECHABS' ACCESS NOT AUTHORIZED

FILE 'SCISEARCH' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Institute for Scientific Information (ISI) (R)

FILE 'DGENE' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'EMBASE' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Elsevier Science B.V. All rights reserved.

FILE 'USPATFULL' ENTERED AT 10:37:06 ON 29 MAR 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'HCAPLUS' ENTERED AT 10:37:06 ON 29 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'JAPIO' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Japanese Patent Office (JPO)

FILE 'FSTA' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 International Food Information Service

FILE 'JICST-EPLUS' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Japan Science and Technology Corporation (JST)

FILE 'FROSTI' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Leatherhead Food Research Association

FILE 'CEN' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 American Chemical Society (ACS)

FILE 'CEABA-VTB' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (c) 2001 DECHEMA eV

FILE 'CA' ENTERED AT 10:37:06 ON 29 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOBUSINESS' ENTERED AT 10:37:06 ON 29 MAR 2001
COPYRIGHT (C) 2001 Biological Abstracts, Inc. (BIOSIS)

=> s cell proliferation

10 FILES SEARCHED...

L1 388590 CELL PROLIFERATION

=> s l1 and (activated [redacted]ood cells)

9 FILES SEARCHED...
L2 6 L1 AND (ACTIVATED BLOOD CELLS)

=> d l2 ti abs ibib tot

L2 ANSWER 1 OF 6 MEDLINE
TI 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells.
AB Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine; PAF) is a potent vasoactive ether lipid produced by **activated blood cells** and endothelial cells.
Vascular smooth muscle cells partially convert exogenous PAF to 1-O-alkyl-2-acetyl-sn-glycerol (AAG), a biologically active diacylglycerol
analogue. AAG is formed rapidly (less than 15 s) after exposure of the smooth muscle cells and does not appear to be a substrate for diacylglycerol kinase in these cells. Although most of the compound is metabolized to 1-O-alkyl-sn-glycerol, a small quantity remains as AAG for greater than or equal to 6 h. AAG inhibits phorbol ester binding, and it is as effective an activator of protein kinase C as diolein in an in vitro
assay. Furthermore, AAG and PAF produce the same pattern of effects on smooth muscle **cell proliferation**. These observations suggest that at least some of the actions of PAF in vascular smooth muscle
may be mediated through the formation of AAG, a stable, bioactive metabolite that appears to function as a diacylglycerol analogue.
ACCESSION NUMBER: 92096480 MEDLINE
DOCUMENT NUMBER: 92096480
TITLE: 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells.
AUTHOR: Stoll L L; Figard P H; Yerram N R; Yorek M A; Spector A A
CORPORATE SOURCE: Department of Biochemistry, University of Iowa, Iowa City 52242.
CONTRACT NUMBER: HL 14230 (NHLBI)
DK 25295 (NIDDK)
SOURCE: CELL REGULATION, (1989 Nov) 1 (1) 13-25.
Journal code: A1U. ISSN: 1044-2030.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204

L2 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
TI 1-O ALKYL-2-ACETYL-SN-GLYCEROL A PLATELET-ACTIVATING FACTOR METABOLITE WITH BIOLOGICAL ACTIVITY IN VASCULAR SMOOTH MUSCLE CELLS.
AB Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine; PAF) is a potent vasoactive ether lipid produced by **activated blood cells** and endothelial cells.
Vascular smooth muscle cells partially convert exogenous PAF to 1-O-alkyl-2-acetyl-sn-glycerol (AAG), a biologically active diacylglycerol
analogue. AAG is formed rapidly (< 15 s) after exposure of the smooth muscle cells and does not appear to be a substrate for diacylglycerol kinase in these cells. Although most of the compound is metabolized to 1-O-alkyl-sn-glycerol, a small quantity remains as AAG for .gtoreq. 6 h. AAG inhibits phorbol ester binding, and it is as effective an activator of

protein kinase C as diolein in an in vitro assay. Furthermore, AAG and PAF produce the same pattern of effects on smooth muscle cell **proliferation**. These observations suggest that at least some of the actions of PAF in vascular smooth muscle may be mediated through the formation of AAG, a stable bioactive metabolite that appears to function as a diacylglycerol analogue.

ACCESSION NUMBER: 1991:46286 BIOSIS
DOCUMENT NUMBER: BA91:24567
TITLE: 1-O ALKYL-2-ACETYL-SN-GLYCEROL A PLATELET-ACTIVATING FACTOR METABOLITE WITH BIOLOGICAL ACTIVITY IN VASCULAR SMOOTH MUSCLE CELLS.
AUTHOR(S): STOLL L L; FIGARD P H; YERRAM N R; YOREK M A; SPECTOR A A
CORPORATE SOURCE: DEP. BIOCHEM., UNIV. IOWA, IOWA CITY, IOWA 52242.
SOURCE: CELL REGUL, (1989) 1 (1), 13-26.
CODEN: CELREQ. ISSN: 1044-2030.
FILE SEGMENT: BA; OLD
LANGUAGE: English

L2 ANSWER 3 OF 6 USPATFULL
TI Peptide inhibitors of fibronectine
AB Cyclic dimeric peptides of formula (I) ##STR1## wherein: peptide 1 and peptide 2 independently represent a tetrapeptide of formula -AA1-AA2-AA3-AA4- juxtaposed in parallel or antiparallel orientation; AA1 is an L or D amino acid selected from Ile, Leu and amino analogues thereof selected from Pro, Gly, Tic and Phe; AA2 is an L amino acid selected from Leu and amino acid analogues thereof selected from Ile, Phe and Val; AA3 is an L amino acid selected from Asp, Glu and amino acid analogues thereof; AA4 is an L amino acid selected from Val and amino acid analogues thereof selected from Leu, Ile, Phe and Cha (cyclohexylalanine); L1 and L2 independently represent linking moieties for linking peptides 1 and 2 to form a cyclic dipeptide; or salts thereof. The cyclic dipeptides inhibit the interaction of vascular cell adhesion molecule-1 and fibronectin with integrin very late antigen 4 and have therapeutic applications such as in rheumatoid arthritis, asthma or multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:27953 USPATFULL
TITLE: Peptide inhibitors of fibronectine
INVENTOR(S): Dutta, Anand Swaroop, Macclesfield, United Kingdom
PATENT ASSIGNEE(S): Zeneca Limited, London, United Kingdom (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 6034057	20000307	
	WO 9702289	19970123	
APPLICATION INFO.:	US 1998-981680	19980106	(8)
	WO 1996-GB1580	19960702	
		19980106	PCT 371 date
		19980106	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1995-13798	19950706
	GB 1996-11470	19960601

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Celsa, Bennett
LEGAL REPRESENTATIVE: Pillsbury Madison & Sutro, LLP
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 11 Drawing Page(s)

LINE COUNT: 1948
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 4 OF 6 USPATFULL
TI Fibronectin adhesion inhibitors
AB Cyclic peptides of formula (1): ##STR1## Wherein: AA1 is an L or D amino acid selected from Ile and Leu or amino acid analogue thereof; AA2 is an L amino acid selected from Leu or amino acids analogue thereof; AA3 is an L amino acid selected from Asp or amino acid analogue thereof containing a carboxy group in its side chain; AA4 is an L amino acid selected from Val or amino acid analogue thereof and; LINKER represents a linking moiety for linking N terminus of AA1 to C terminus of AA4 to form a cyclic peptide containing a heterocyclic ring having 17 to 30 members. The cyclic peptides inhibit the interaction of vascular cell adhesion molecule-1 and fibronectin with integrin very late antigen 4 and have therapeutic applications such as in rheumatoid arthritis or multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:27952 USPATFULL		
TITLE:	Fibronectin adhesion inhibitors		
INVENTOR(S):	Dutta, Anand Swaroop, Macclesfield, United Kingdom		
PATENT ASSIGNEE(S):	Zeneca Limited, London, United Kingdom (non-U.S. corporation)		
	NUMBER	DATE	
PATENT INFORMATION:	US 6034056	20000307	
	WO 9620216	19960704	
APPLICATION INFO.:	US 1997-860248	19970624	(8)
	WO 1995-GB2992	19951221	
		19970624	PCT 371 date
		19970624	PCT 102(e) date
	NUMBER	DATE	
PRIORITY INFORMATION:	GB 1994-26254	19941224	
	GB 1995-5905	19950324	
	GB 1995-13904	19950707	
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Tsang, Cecilia J.		
LEGAL REPRESENTATIVE:	Phillsbury Madison & Sutro, LLPIntellectual Property Group		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	16 Drawing Figure(s); 22 Drawing Page(s)		
LINE COUNT:	3750		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2001 ACS
TI 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells
AB Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine; PAF) is a potent vasoactive ether lipid produced by **activated blood cells** and endothelial cells. Vascular smooth muscle cells partially convert exogenous PAF to 1-O-alkyl-2-acetyl-sn-glycerol (AAG), a biol. active diacylglycerol analog. AAG is formed rapidly (<15 s) after exposure of the smooth muscle cells and does not appear to be a substrate for diacylglycerol kinase in these cells. Although most of the compd. is metabolized to 1-O-alkyl-sn-glycerol, a small quantity remains as AAG for >6 h. AAG

inhibits phorbol ester binding, and it is as effective an activator of protein kinase C as the diolein in an in vitro assay. Furthermore, AAG and PAF produce the same pattern of effects on smooth muscle **cell proliferation**. Apparently, at least some of the actions of PAF in vascular smooth muscle may be mediated through the formation of AAG, a stable, bioactive metabolite that appears to function as a diacylglycerol analog.

ACCESSION NUMBER: 1990:116242 HCAPLUS
DOCUMENT NUMBER: 112:116242
TITLE: 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells
AUTHOR(S): Stoll, Lynn L.; Figard, Paul H.; Yerram, Nagender R.; Yorek, Mark A.; Spector, Arthur A.
CORPORATE SOURCE: Dep. Biochem., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Cell Regul. (1989), 1(1), 13-25
CODEN: CELREQ; ISSN: 1044-2030
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 6 OF 6 CA COPYRIGHT 2001 ACS
TI 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells
AB Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine; PAF) is a potent vasoactive ether lipid produced by **activated blood cells** and endothelial cells. Vascular smooth muscle cells partially convert exogenous PAF to 1-O-alkyl-2-acetyl-sn-glycerol (AAG), a biol. active diacylglycerol analog. AAG is formed rapidly (<15 s) after exposure of the smooth muscle cells and does not appear to be a substrate for diacylglycerol kinase in these cells. Although most of the compd. is metabolized to 1-O-alkyl-sn-glycerol, a small quantity remains as AAG for >6 h. AAG inhibits phorbol ester binding, and it is as effective an activator of protein kinase C as the diolein in an in vitro assay. Furthermore, AAG and PAF produce the same pattern of effects on smooth muscle **cell proliferation**. Apparently, at least some of the actions of PAF in vascular smooth muscle may be mediated through the formation of AAG, a stable, bioactive metabolite that appears to function as a diacylglycerol analog.

ACCESSION NUMBER: 112:116242 CA
TITLE: 1-O-alkyl-2-acetyl-sn-glycerol: a platelet-activating factor metabolite with biological activity in vascular smooth muscle cells
AUTHOR(S): Stoll, Lynn L.; Figard, Paul H.; Yerram, Nagender R.; Yorek, Mark A.; Spector, Arthur A.
CORPORATE SOURCE: Dep. Biochem., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Cell Regul. (1989), 1(1), 13-25
CODEN: CELREQ; ISSN: 1044-2030
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 10:36:05 ON 29 MAR 2001)

FILE 'MEDLINE, BIOSIS, BIOTECHDS, SCISEARCH, DGENE, EMBASE, USPATFULL, WPIDS, HCAPLUS, JAPIO, FSTA, JICST-EPLUS, FROSTI, CEN, CEABA-VTB, CA,

```
    BIOBUSINESS' ENTERED AT 10:37:06 ON 29 MAR 2001
L1       388590 S CELL PROLIFERATION
L2            6 S L1 A[redacted](ACTIVATED BLOOD CELLS)

=> s l1 and (method of reversing proliferation?)

  11 FILES SEARCHED...
L3            0 L1 AND (METHOD OF REVERSING PROLIFERATION?)

=> s l1 and (lactacystin)

L4          102 L1 AND (LACTACYSTIN)

=> s l4 and method

L5            9 L4 AND METHOD

=> s cyclosporin A

   5 FILES SEARCHED...
   7 FILES SEARCHED...
  10 FILES SEARCHED...
L6        76319 CYCLOSPORIN A

=> s rapamycin

   5 FILES SEARCHED...
L7        14497 RAPAMYCIN

=> s l7 and l6

L8         3147 L7 AND L6

=> s FK506

L9        18485 FK506

=> s l8 and l9

  11 FILES SEARCHED...
L10        1471 L8 AND L9

=> s l10 and immunosuppressive drug

L11          83 L10 AND IMMUNOSUPPRESSIVE DRUG

=> s protease inhibitor

   6 FILES SEARCHED...
L12       57835 PROTEASE INHIBITOR

=> d his


     (FILE 'HOME' ENTERED AT 10:36:05 ON 29 MAR 2001)

     FILE 'MEDLINE, BIOSIS, BIOTECHDS, SCISEARCH, DGENE, EMBASE, USPATFULL,
     WPIDS, HCAPLUS, JAPIO, FSTA, JICST-EPLUS, FROSTI, CEN, CEABA-VTB, CA,
     BIOBUSINESS' ENTERED AT 10:37:06 ON 29 MAR 2001
L1       388590 S CELL PROLIFERATION
L2            6 S L1 AND (ACTIVATED BLOOD CELLS)
L3            0 S L1 AND (METHOD OF REVERSING PROLIFERATION?)
L4          102 S L1 AND (LACTACYSTIN)
L5            9 S L4 AND METHOD
```

L6 76319 S CYCLOSPORIN A
L7 14497 S RAPAMYCIN
L8 3147 S L7 AND L6
L9 18485 S FK506
L10 1471 S L8 AND L9
L11 83 S L10 AND IMMUNOSUPPRESSIVE DRUG
L12 57835 S PROTEASE INHIBITOR

=> s l5 ti abs ibib tot

MISSING OPERATOR L5 TI
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l5 ti abs ibib tot

L5 ANSWER 1 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS
TI Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AB Vascular smooth muscle cells exhibit a striking plasticity and are able to change from a differentiated, contractile phenotype to a more immature, synthetic phenotype. This includes a prominent structural reorganization with loss of myofilaments and construction of a large secretory apparatus.
As a result, the cells lose their contractility and become able to migrate, proliferate, and secrete extracellular matrix components. In vivo, this phenotypic shift is a chief factor behind the involvement of smooth muscle cells in formation of atherosclerotic and restenotic lesions. Here, the effects of the proteasome inhibitors carbobenzoxy-leucyl-leucyl-leucinal, N-acetyl-leucyl-leucyl-norleucinal, and **lactacystin** on the morphologic structure and growth of rat aortic smooth muscle cells in primary culture were examined. Electron microscopic analysis revealed that the volume density of myofilaments was higher and the volume density of the endoplasmic reticulum and the Golgi complex was lower incells exposed to these drugs than in solvent-treated controls. Moreover, diffuse material representing incompletely degraded proteins gathered in the cytoplasm of exposed cells. Similar material was also found in lysosomes. Immunogold staining showed a positive reaction in the diffuse cytoplasmic aggregates with antibodies against ubiquitin-protein conjugates and proteasomes, whereas the material collecting in lysosomes reacted only with those against ubiquitin-protein conjugates. Moreover, weak staining for smooth muscle alpha-actin was noted in the cytoplasmic aggregates. Otherwise, reactivity for this protein was concentrated in myofilaments. In addition to the effects on cell structure described above, the proteasome inhibitors blocked cell multiplication. This was probably due to a decreased rate of transition into a synthetic state as well as direct interference with cell cycle progression in synthetic cells. These observations suggest that proteasomes have the major responsibilityfor protein degradation during transition of smooth muscle cells from a contractile to a synthetic phenotype. If proteasome activity is inhibited, undegraded material accumulates in the cytoplasm and is only partially taken up into lysosomes for digestion. These findings raise the possibility that proteasome inhibitors may have a beneficial effect on vascular pathologies associated with phenotypic modulation and proliferation of smooth muscle cells.
ACCESSION NUMBER: 1999:510184 BIOSIS
DOCUMENT NUMBER: PREV199900510184
TITLE: Effects of proteasome and calpain inhibitors on the

structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AUTHOR(S): Thyberg, Johan (1); Blomgren, Karin
CORPORATE SOURCE: (1) Department of Cell and Molecular Biology, Karolinska Institut, S-171 77, Stockholm Sweden
SOURCE: Laboratory Investigation, (Sept., 1999) Vol. 79, No. 9, pp. 1077-1088.
ISSN: 0023-6837.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

bad date

L5 ANSWER 2 OF 9 USPATFULL
TI **Lactacystin** analogs
AB Compounds related to **lactacystin** and **lactacystin** .beta.-lactone, pharmaceutical compositions containing the compounds, and methods of use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:153855 USPATFULL
TITLE: **Lactacystin** analogs
INVENTOR(S): Fenteany, Gabriel, Cambridge, MA, United States
Jamison, Timothy F., Cambridge, MA, United States
Schreiber, Stuart L., Boston, MA, United States
Standaert, Robert F., Arlington, MA, United States
PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6147223	20001114
APPLICATION INFO.:	US 1995-468408	19950606 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-421583, filed on 12 Apr 1995
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Gerstl, Robert
LEGAL REPRESENTATIVE: Hale and Dorr LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 9 USPATFULL
TI Inhibition of 26S and 20S proteasome by indanones
AB This invention is novel indanone compositions useful for inhibiting **cell proliferation** disorders in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:121530 USPATFULL
TITLE: Inhibition of 26S and 20S proteasome by indanones
INVENTOR(S): Lum, Robert T., Palo Alto, CA, United States
Schow, Steven R., Redwood City, CA, United States
Joly, Alison, San Mateo, CA, United States
Kerwar, Suresh, Westchester, NY, United States
Nelson, Marek G., Sunol, CA, United States
Wick, Michael M., Chestnut Hill, MA, United States
PATENT ASSIGNEE(S): CV Therapeutics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6117887	20000912
APPLICATION INFO.:	US 1998-88581	19980602 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-719042, filed on 24 Sep 1996, now patented, Pat. No. US 5834487
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 976
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 9 USPATFULL
TI .alpha.-ketoamide inhibitors of 20S proteasome
AB .alpha.-ketoamide compounds useful for treating disorders mediated by 20S proteasome in mammals having the following formula: wherein X.sub.2 is Ar or Ar--X.sub.3 wherein X.sub.3 is --C.dbd.O, or --CH.sub.2 CO--, and wherein Ar is phenyl, substituted phenyl, indole, substituted indoles, and any other heteroaryls; R.sub.1, and R.sub.2 are each individually selected from the side chains of the known natural .alpha.-amino acids and unnatural amino acids, hydrogen, 1-10 carbon linear and branched alkyl, 1-10 carbon linear and branched substituted alkyl, aryl, substituted aryl, 1-10 carbon linear, branched substituted aryl, alkoxyaryl, 3-8 carbon cycloalkyl, heterocycle substituted heterocycle, heteroaryl and substituted heteroaryl; X.sub.1 is selected from hydroxide, monoalkylamino, dialkylamino, alkoxide, arylkoxide and ##STR1## wherein X.sub.4 is hydroxide, arylamino, monoalkylamino, dialkylamino, alkoxide, or arylalkoxide; and R.sub.3 is selected from the known natural .alpha.-amino acids, unnatural amino acids, hydrogen, 1-10 carbon linear and branched alkyl, 1-10 carbon linear and branched substituted alkyl, aryl, substituted aryl, 1-10 carbon linear and branched substituted aryl, alkoxyaryl, 3-8 carbon cycloalkyl, heterocycle, substituted heterocycle, heteroaryl and substituted heteroaryl.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:74414 USPATFULL
TITLE: .alpha.-ketoamide inhibitors of 20S proteasome
INVENTOR(S): Wang, Lisa, Burlingame, CA, United States
Lum, Robert T., Palo Alto, CA, United States
Schow, Steven R., Redwood City, CA, United States
Joly, Alison, San Mateo, CA, United States
Kerwar, Suresh, Westchester, NY, United States
Wick, Michael M, Chestnut Hill, MA, United States
PATENT ASSIGNEE(S): CV Therapeutics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6075150	20000613
APPLICATION INFO.:	US 1998-13365	19980126 (9)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Davis, Brian J.
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 1523
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 9 USPATFULL
TI Treatment of tumors by arginine deprivation
AB **Method**, compositions and apparatus for the treatment of tumors by systemic deprivation of an essential amino acid, preferably of arginine, by extracorporeal treatment of the patient's blood

characterized by molecular exchange between the blood and a dialyzing fluid which contains most of the essential low-molecular substances found in blood plasma with the exception of at least one of the essential amino acids. The release of muscular protein amino acids can be limited by use of an insulin/glucose clamp. The treatment process can
be used in conjunction with chemotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:159917 USPATFULL	
TITLE:	Treatment of tumors by arginine deprivation	
INVENTOR(S):	Tepic, Slobodan, Oberestrasse 20, CH-7270 Davos, Switzerland	
	Pyk, Pawel, Oberestrasse 20, CH-7270 Davos, Switzerland	
	NUMBER	DATE
PATENT INFORMATION:	US 5851985	19981222
APPLICATION INFO.:	US 1996-698876	19960816 (8)
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Witz, Jean C.	
LEGAL REPRESENTATIVE:	Orzechowski, Karen LeeNath and Associates	
NUMBER OF CLAIMS:	13	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)	
LINE COUNT:	976	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 9 USPATFULL
TI Inhibition of 26S and 20S proteasome by indanones
AB This invention is a **method** for inhibiting **cell proliferation** using indanones.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:138919 USPATFULL	
TITLE:	Inhibition of 26S and 20S proteasome by indanones	
INVENTOR(S):	Lum, Robert T., Palo Alto, CA, United States	
	Schow, Steven R., Redwood City, CA, United States	
	Joly, Alison, San Mateo, CA, United States	
	Kerwar, Suresh, Westchester, NY, United States	
	Nelson, Marek G., Sunol, CA, United States	
	Wick, Michael M., Chestnut Hill, MA, United States	
PATENT ASSIGNEE(S):	CV Therapeutics, Palo Alto, CA, United States (U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5834487	19981110
APPLICATION INFO.:	US 1996-719042	19960924 (8)
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Criares, Theodore J.	
LEGAL REPRESENTATIVE:	McDonnell Boehnen Hulbert & Berghoff	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)	
LINE COUNT:	1104	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 9 USPATFULL
TI **Lactacystin** analogs
AB Described herein are compounds related to **lactacystin** and **lactacystin** .beta.-lactone, pharmaceutical compositions containing the compounds, and methods of use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:58182 USPATFULL
TITLE: **Lactacystin** analogs
INVENTOR(S): Fenteany, Gabriel, Cambridge, MA, United States
Jamison, Timothy F., Cambridge, MA, United States
Schreiber, Stuart L., Boston, MA, United States
Standaert, Robert F., Arlington, MA, United States
PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5756764	19980526
APPLICATION INFO.:	US 1995-466468	19950606 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-421583, filed on 12 Apr 1995
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Stockton, Laura L.
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 2392
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2001 ACS
TI The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening **method**
AB The present invention relates to compns. comprising proteasome inhibitors, such as lactocystin and analogs thereof. These compns. are used for the following purposes: (1) to disrupt mitochondrial function (useful against cancer, inflammation, adverse immune reaction and hyperthyroidism), (2) to disrupt nitric oxide synthesis (useful against inflammation and septic shock), and (3) to reverse ongoing adverse immune reactions, such as autoimmune diseases and graft rejection. In the latter case, the compns. are administered once the patient's T cells are mostly activated. Proteasome inhibitors can also be combined with immunosuppressive drugs, e.g. rapamycin, cyclosporin A, and FK506. Finally, a **method** for screening a compd. having a proteasome inhibition activity is also disclosed and claimed.
ACCESSION NUMBER: 1999:311103 HCAPLUS
DOCUMENT NUMBER: 130:332911
TITLE: The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening **method**
INVENTOR(S): Wu, Jiangping; Wang, Xin
PATENT ASSIGNEE(S): Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Can.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9922729	A1	19990514	WO 1998-CA1010	19981029

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP,

KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9897318	A1	19990524	AU 1998-97318	19981029
EP 967976	A1	20000105	EP 1998-951135	19981029

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: CA 1997-2219867 19971031
WO 1998-CA1010 19981029

REFERENCE COUNT: 15
REFERENCE(S):
(1) Conner, E; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1997, V282(3), P1615 HCAPLUS
(2) Cui, H; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1997, V94(14), P7515 HCAPLUS
(3) Griscavage, J; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1996, V93(8), P3308 HCAPLUS
(4) Harvard College; WO 9417816 A 1994 HCAPLUS
(5) Harvard College; WO 9632105 A 1996 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 9 CA COPYRIGHT 2001 ACS
TI The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening **method**
AB The present invention relates to compns. comprising proteasome inhibitors, such as lactocystin and analogs thereof. These compns. are used for the following purposes: (1) to disrupt mitochondrial function (useful against cancer, inflammation, adverse immune reaction and hyperthyroidism), (2) to disrupt nitric oxide synthesis (useful against inflammation and septic shock), and (3) to reverse ongoing adverse immune reactions, such as autoimmune diseases and graft rejection. In the latter case, the compns. are administered once the patient's T cells are mostly activated. Proteasome inhibitors can also be combined with immunosuppressive drugs, e.g. rapamycin, cyclosporin A, and FK506. Finally, a **method** for screening a compd. having a proteasome inhibition activity is also disclosed and claimed.
ACCESSION NUMBER: 130:332911 CA
TITLE: The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening **method**
INVENTOR(S): Wu, Jiangping; Wang, Xin
PATENT ASSIGNEE(S): Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Can.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9922729	A1	19990514	WO 1998-CA1010	19981029

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP,

KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA,
UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9897318	A1	19990524	AU 1998-97318	19981029	
EP 967976	A1	20000105	EP 1998-951135	19981029	

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

PRIORITY APPLN. INFO.:	CA 1997-2219867	19971031
	WO 1998-CA1010	19981029

REFERENCE COUNT: 15
REFERENCE(S):
(1) Conner, E; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1997, V282(3), P1615 CA
(2) Cui, H; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1997, V94(14), P7515 CA
(3) Griscavage, J; PROCEEDINGS OF THE NATIONAL ACADEMY
OF SCIENCES OF THE UNITED STATES OF AMERICA 1996, V93(8), P3308 CA
(4) Harvard College; WO 9417816 A 1994 CA
(5) Harvard College; WO 9632105 A 1996 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 10:36:05 ON 29 MAR 2001)

FILE 'MEDLINE, BIOSIS, BIOTECHDS, SCISEARCH, DGENE, EMBASE, USPATFULL, WPIDS, HCAPLUS, JAPIO, FSTA, JICST-EPLUS, FROSTI, CEN, CEABA-VTB, CA, BIOBUSINESS' ENTERED AT 10:37:06 ON 29 MAR 2001

L1	388590	S	CELL PROLIFERATION
L2	6	S	L1 AND (ACTIVATED BLOOD CELLS)
L3	0	S	L1 AND (METHOD OF REVERSING PROLIFERATION?)
L4	102	S	L1 AND (LACTACYSTIN)
L5	9	S	L4 AND METHOD
L6	76319	S	CYCLOSPORIN A
L7	14497	S	RAPAMYCIN
L8	3147	S	L7 AND L6
L9	18485	S	FK506
L10	1471	S	L8 AND L9
L11	83	S	L10 AND IMMUNOSUPPRESSIVE DRUG
L12	57835	S	PROTEASE INHIBITOR

=> s lactacystin

L13 2614 LACTACYSTIN

=> s proteasome inhibitor

5 FILES SEARCHED...
L14 2435 PROTEASOME INHIBITOR

=> s l13 and l14

L15 787 L13 AND L14

=> s l15 and l11

L16 0 L15 AND L11

=> s l11 and l1

L17 21 L11 AND L1

=> s l15 and l1

L18 30 L15 AND L1

=> s l17 and l18

L19 0 L17 AND L18

=> d l17 ti abs ibib to

'TO' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files. Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):end

=> d l17 ti abs ibib tot

L17 ANSWER 1 OF 21 MEDLINE
TI New **immunosuppressive drug** PNU156804 blocks
IL-2-dependent proliferation and NF-kappa B and AP-1 activation.
AB We had previously shown that the drug undecylprodigiosin (UP) blocks human
lymphocyte proliferation in vitro. We have now investigated the mechanism
of action of a new analogue of UP, PNU156804, which shows a more favorable
activity profile than UP in mice. We demonstrate here that the biological
effect of PNU156804 in vitro is indistinguishable from UP: PNU156804
blocks human T **cell proliferation** in mid-late G1, as
determined by cell cycle analysis, expression of cyclins, and
cyclin-dependent kinases and retinoblastoma phosphorylation. In addition,
we show that PNU156804 does not block significantly the induction of
either IL-2 or IL-2R alpha- and gamma-chains but inhibits IL-2-dependent T
cell proliferation. We have investigated several
molecular pathways that are known to be activated by IL-2 in T cells. We
show that PNU156804 does not inhibit c-myc and bcl-2 mRNA induction. On
the other hand, PNU156804 efficiently inhibits the activation of the
NF-kappa B and AP-1 transcription factors. PNU156804 inhibition of
NF-kappa B activation is due to the inhibition of the degradation of I
kappa B-alpha and I kappa B-beta. PNU156804 action is restricted to some
signaling pathways; it does not affect NF-kappa B activation by PMA in T
cells but blocks that induced by CD40 cross-linking in B lymphocytes. We
conclude that the prodigiosin family of immunosuppressants is a new family
of molecules that show a novel target specificity clearly distinct from
that of other immunosuppressive drugs such as **cyclosporin A**, **FK506**, and **rapamycin**.
ACCESSION NUMBER: 1999288066 MEDLINE
DOCUMENT NUMBER: 99288066
TITLE: New **immunosuppressive drug** PNU156804
blocks IL-2-dependent proliferation and NF-kappa B and AP-1
activation.
AUTHOR: Mortellaro A; Songia S; Gnocchi P; Ferrari M; Fornasiero C;

D'Alessio R; Isetta A; Colotta F; Golay J
CORPORATE SOURCE: Department of Immunology and Cell Biology, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy.
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Jun 15) 162 (12) 7102-9.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199909

L17 ANSWER 2 OF 21 MEDLINE
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AB We previously demonstrated the capacity of the hydroxylamine metabolite of sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. We studied the interaction of SMX-HA with the immuno-suppressants **cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohaemaglutinin, and phorbol myristate acetate and proliferation was determined by cellular uptake of 3H-thymidine. Using median-effect analysis and concentration reduction index calculations to assess **immunosuppressive drug** interactions, we produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concentration reductions at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, respectively, were observed with 25 microM SMX-HA, and this effect was not associated with reduced cell viability. SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concentrations also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein production, which suggests that signaling events proximal to cytokine production are not affected by the metabolite. Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.
ACCESSION NUMBER: 97256701 MEDLINE
DOCUMENT NUMBER: 97256701
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AUTHOR: Hess D A; Bird I A; Almawi W Y; Rieder M J
CORPORATE SOURCE: Department of Paediatrics, Robarts Research Institute, University of Western Ontario, London, Canada.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Apr) 281 (1) 540-8.
Journal code: JP3. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707

L17 ANSWER 3 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AB We previously demonstrated the capacity of the hydroxylamine metabolite of

sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. We studied the interaction of SMX-HA with the immuno-suppressan[redacted]**cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohaemagglutinin, and phorbol myristate acetate and proliferation was determined by cellular uptake of 3H-thymidine. Using median-effect analysis and concentration reduction index calculations to assess **immunosuppressive drug** interactions, we produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concentration reductions at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, respectively, were observed with 25 mu-M SMX-HA, and this effect was not associated with reduced cell viability. SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concentrations also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein production, which suggests that signaling events proximal to cytokine production are not affected by the metabolite. Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.

ACCESSION NUMBER: 1997:216446 BIOSIS
DOCUMENT NUMBER: PREV199799522950
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AUTHOR(S): Hess, David A.; Bird, Ingrid A.; Almawi, Wassim Y.; Rieder, Michael J. (1)
CORPORATE SOURCE: (1) Molecular Virol. Gene Therapy Group, Robarts Res. Inst., Univ. Western Ontario, 100 Perth Dr., London, Ontario N6A 5K8 Canada
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1997) Vol. 281, No. 1, pp. 540-548. ISSN: 0022-3565.
DOCUMENT TYPE: Article
LANGUAGE: English

L17 ANSWER 4 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
TI New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-kappa B and AP-1 activation
AB We had previously shown that the drug undecylprodigiosin (UP) blocks human lymphocyte proliferation in vitro. We have now investigated the mechanism of action of a new analogue of UP, PNU156804, which shows a more favorable activity profile than UP in mice. We demonstrate here that the biological effect of PNU156804 in vitro is indistinguishable from UP: PNU156804 blocks human T **cell proliferation** in mid-late G(1), as determined by cell cycle analysis, expression of cyclins, and cyclin-dependent kinases and retinoblastoma phosphorylation, In addition, we show that PNU156804 does not block significantly the induction of either IL-2 or IL-2R alpha- and gamma-chains but inhibits IL-2-dependent T **cell proliferation**. We have investigated several molecular pathways that are known to be activated by IL-2 in T cells. We show that PNU156804 does ndt inhibit c-myc and bcl-2mRNA induction. On the other hand, PNU156804 efficiently inhibits the activation of the NF-kappa B and AP-1 transcription factors. PNU156804 a inhibition of NF-kappa B activation is due to the inhibition of the degradation of I kappa B-alpha and I kappa B-beta, PNU156804 action is restricted to some signaling pathways; it does not affect:NF-kappa B activation by PMA in T cells but blocks that induced by CD40 cross-linking

in B lymphocytes, We conclude that the prodigiosin family of immunosuppressants is a new family:of molecules that show a novel target specificity clearly distinct from that of other immunosuppressive drugs-such as **cyclosporin A**, **FK506**; and **rapamycin**.

ACCESSION NUMBER: 1999:462988 SCISEARCH
THE GENUINE ARTICLE: 205BT
TITLE: New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-kappa B and AP-1 activation
AUTHOR: Mortellaro A; Songia S; Gnocchi P; Ferrari M; Fornasiero C; DAlessio R; Isetta A; Colotta F; Golay J (Reprint)
CORPORATE SOURCE: INST RICERCHE FARMACOL MARIO NEGRI, DEPT IMMUNOL & CELL BIOL, VIA ERITREA 62, I-20157 MILAN, ITALY (Reprint); INST RICERCHE FARMACOL MARIO NEGRI, DEPT IMMUNOL & CELL BIOL, I-20157 MILAN, ITALY; PHARMACIA & UPJOHN INC, RES CTR, DEPT PHARMACOL, NERVIANO, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: JOURNAL OF IMMUNOLOGY, (15 JUN 1999) Vol. 162, No. 12, pp. 7102-7109.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L17 ANSWER 5 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**

AB We previously demonstrated the capacity of the hydroxylamine metabolite of sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. We studied the interaction of SMX-HA with the immuno-suppressants **cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohaemaglutinin, and phorbol myristate acetate and proliferation was determined by cellular uptake of H-3-thymidine, Using median-effect analysis and concentration reduction index calculations to assess **immunosuppressive drug** interactions, we produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concentration reductions at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, respectively, were observed with 25 mu M SMX-HA, and this effect was not associated with reduced cell viability, SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concentrations also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein production, which suggests that signaling events proximal to cytokine production are not affected by the metabolite, Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.

ACCESSION NUMBER: 97:321598 SCISEARCH
THE GENUINE ARTICLE: WU522
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**,

inhibiting T-**cell proliferation**

AUTHOR: Hess D A; Bird I A; Almawi W Y; Rieger M J (Reprint)

CORPORATE SOURCE: UNIV WESTERN ONTARIO, ROBARTS RES INST, MOL VIROL & GENE THERAPY GRP, 100 PERTH DR, LONDON, ON N6A 5K8, CANADA (Reprint); UNIV WESTERN ONTARIO, ROBARTS RES INST, DEPT PAEDIAT & PHARMACOL & TOXICOL, LONDON, ON N6A 5K8, CANADA

COUNTRY OF AUTHOR: CANADA

SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (APR 1997) Vol. 281, No. 1, pp. 540-548.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0022-3565.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L17 ANSWER 6 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

TI New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation.

AB We had previously shown that the drug undecylprodigiosin (UP) blocks human lymphocyte proliferation in vitro. We have now investigated the mechanism of action of a new analogue of UP, PNU156804, which shows a more favorable activity profile than UP in mice. We demonstrate here that the biological effect of PNU156804 in vitro is indistinguishable from UP: PNU156804 blocks human T **cell proliferation** in mid-late G1, as determined by cell cycle analysis, expression of cyclins, and cyclin-dependent kinases and retinoblastoma phosphorylation. In addition, we show that PNU156804 does not block significantly the induction of either IL-2 or IL-2R .alpha.- and .gamma.-chains but inhibits IL-2-dependent T **cell proliferation**. We have investigated several molecular pathways that are known to be activated by IL-2 in T cells. We show that PNU156804 does not inhibit c-myc and bcl-2 mRNA induction. On the other hand, PNU156804 efficiently inhibits the activation of the NF-.kappa.B and AP-1 transcription factors. PNU156804 inhibition of NF-.kappa.B activation is due to the inhibition of the degradation of I.kappa.B-.alpha. and I.kappa.B-.beta.. PNU156804 action is restricted to some signaling pathways; it does not affect NF-.kappa.B activation by PMA in T cells but blocks that induced by CD40 cross-linking in B lymphocytes. We conclude that the prodigiosin family of immunosuppressants is a new family of molecules that show a novel target specificity clearly distinct from that of other immunosuppressive drugs such as **cyclosporin A**, **FK506**, and **rapamycin**.

ACCESSION NUMBER: 1999209974 EMBASE

TITLE: New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation.

AUTHOR: Mortellaro A.; Songia S.; Gnocchi P.; Ferrari M.; Fornasiero C.; D'Alessio R.; Isetta A.; Colotta F.; Golay J.

CORPORATE SOURCE: Dr. J. Golay, Ist. Ric. Farmacol. 'Mario Negri', via Eritrea 62, 20157 Milan, Italy. Golay@irfmn.mnegri.it

SOURCE: Journal of Immunology, (15 Jun 1999) 162/12 (7102-7109).
Refs: 51
ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L17 ANSWER 7 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AB We previously demonstrated the capacity of the hydroxylamine metabolite of sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. We studied the interaction of SMX-HA with the immuno-suppressants **cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohaemaglutinin, and phorbol myristate acetate and proliferation was determined by cellular uptake of 3H- thymidine. Using median-effect analysis and concentration reduction index calculations to assess **immunosuppressive drug** interactions, we produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concentration reductions at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, respectively, were observed with 25 .mu.M SMX-HA, and this effect was not associated with reduced cell viability. SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concentrations also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein production, which suggests that signaling events proximal to cytokine production are not affected by the metabolite. Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.
ACCESSION NUMBER: 97144666 EMBASE
DOCUMENT NUMBER: 1997144666
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**.
AUTHOR: Hess D.A.; Bird I.A.; Almawi W.Y.; Rieder M.J.
CORPORATE SOURCE: Dr. M.J. Rieder, MVGTG, Robarts Research Institute, University of Western Ontario, 100 Perth Dr., London, Ont. N6A 5K8, Canada
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1997) 281/1 (540-548).
Refs: 43
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L17 ANSWER 8 OF 21 USPATFULL
TI Use of rosmarinic acid and derivatives thereof as an immunosuppressant or an inhibitor of SH2-mediated processes
AB The present invention relates to use of rosmarinic acid and/or derivatives thereof as immunosuppressive agents and/or as inhibitor of SH2 domain function. Disclosed in the present invention is that rosmarinic acid and derivatives thereof specifically inhibit the binding of ligand peptides to Lck SH2 domain, disturb the Lck-mediated signal

transduction in T cells, also inhibit cytoline gene expression, and suppress immune responses in the transplanted tissue. These activities of rosmarinic acid and derivatives thereof support their applicability to treatment, prevention and/or diagnosis of graft rejection, GVHD, autoimmune diseases, inflammatory diseases, etc.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:146409 USPATFULL
TITLE:	Use of rosmarinic acid and derivatives thereof as an immunosuppressant or an inhibitor of SH2-mediated processes
INVENTOR(S):	Hur, Eun Mi, Kyonggi-do, Korea, Republic of Choi, Young Bong, Kyonggi-do, Korea, Republic of Park, Changwon, Kyonggi-do, Korea, Republic of Lee, Jongsung, Seoul, Korea, Republic of Park, Dongsu, Kyonggi-do, Korea, Republic of Yun, Yungdae, Seoul, Korea, Republic of Lee, Keun Hyeung, Seoul, Korea, Republic of Oh, Jong-Eun, Seoul, Korea, Republic of Ahn, Soon Choul, Taejon-si, Korea, Republic of Lee, Hyun Sun, Taejon-si, Korea, Republic of Ahn, Jong Sok, Taejon-si, Korea, Republic of Jung, Soo Il, Kyonggi-do, Korea, Republic of
PATENT ASSIGNEE(S):	Mogam Biotechnology Research Institute, Korea, Republic of (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6140363	20001031
APPLICATION INFO.:	US 1999-312405	19990514 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	KR 1998-17741	19980516
	KR 1999-15989	19990504

DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Reamer, James H.
LEGAL REPRESENTATIVE:	Gates & Cooper
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1,9
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	1179

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 9 OF 21 USPATFULL

TI Indolyl-pyrrolydenemethylpyrrole derivatives and process for their preparation

AB The present invention relates to substituted (1H-indol-2-yl)-5[(2H-pyrrol-2-ylidene) methyl]-1H-pyrrole compounds and their use as immunomodulating agents, to the preparation of the compounds and to pharmaceutical compositions comprising them.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:70876 USPATFULL
TITLE:	Indolyl-pyrrolydenemethylpyrrole derivatives and process for their preparation
INVENTOR(S):	D'Alessio, Roberto, Cinisello Balsamo, Italy Tibolla, Marcellino, Senago, Italy Bargiotti, Alberto, Milan, Italy Isetta, Anna Maria, Rho, Italy Ferrari, Mario, Milan, Italy Colotta, Francesco, Milan, Italy
PATENT ASSIGNEE(S):	Pharmacia & Upjohn S.p.A., Milan, Italy (non-U.S.

corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 6071947	20000606	
	WO 9840380	19980917	
APPLICATION INFO.:	US 1998-147249	19981112	(9)
	WO 1998-EP1285	19980227	
		19981112	PCT 371 date
		19981112	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1997-5035	19970311

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Oswecki, Jane C.
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 1187
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 10 OF 21 USPATFULL
TI Use of hyaluronic acid as an immunosuppressant
AB A pharmaceutical formulation of hyaluronic acid is administered to a patient suffering from undesirable T cellactivity. The hyaluronic acid inhibits T cell activity at doses that are well-tolerated by the recipient. Conditions suitable for treatment include graft vs. host disease, graft rejection and certain autoimmune diseases having a T cell component.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:4803 USPATFULL
TITLE: Use of hyaluronic acid as an immunosuppressant
INVENTOR(S): Lussow, Alexander R., Menlo Park, CA, United States
Buelow, Roland, Palo Alto, CA, United States
PATENT ASSIGNEE(S): SangStat Medical Corporation, Fremont, CA, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 6013641	20000111	
APPLICATION INFO.:	US 1996-721835	19960927	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-4468	19950928 (60)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Wortman, Donna
ASSISTANT EXAMINER: Brumback, Brenda G.
LEGAL REPRESENTATIVE: Trecartin, Richard F.; Lorenz, Todd A.Albritton & Herbert LLP
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 593
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 11 OF 21 USPATFULL
TI Immunosuppressive compounds and methods
AB Compounds and methods for use in immunosuppressive and anti-inflammatory

treatment, and for inhibiting male fertility, are described. The compounds are triptolide analogs with improved water solubility and low toxicity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:121418 USPATFULL		
TITLE:	Immunosuppressive compounds and methods		
INVENTOR(S):	Qi, You Mao, Los Altos, CA, United States		
	Musser, John H., San Carlos, CA, United States		
	Fidler, John M., Oakland, CA, United States		
PATENT ASSIGNEE(S):	Pharmagenesis, Inc., Palo Alto, CA, United States (U.S.		
	corporation)		
	NUMBER	DATE	
PATENT INFORMATION:	US 5962516	19991005	
	WO 9731921	19970904	
APPLICATION INFO.:	US 1999-142128	19990125	(9)
	WO 1997-US3202	19970228	
		19990125	PCT 371 date
		19990125	PCT 102(e) date
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Reamer, James H.		
LEGAL REPRESENTATIVE:	Gorthey, LeeAnn; Powers, Vincent M.		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1,4		
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 8 Drawing Page(s)		
LINE COUNT:	1309		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 12 OF 21 USPATFULL

TI Immunotherapy composition and method

AB A composition for use in immunosuppression therapy is disclosed. The composition includes an immunosuppressant drug, such as **cyclosporin A**, and an ethanol extract of the root xylem of Tripterygium wilfordii. The extract is effective alone, or in combination with such an immunosuppressant, in the treatment of transplantation rejection. Also disclosed is a method of immunosuppression that includes administering to a subject a pharmaceutically effective amount of an immunosuppressant drug and an extract of the type above, in an amount effective to potentiate the action of the drug.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:150472 USPATFULL		
TITLE:	Immunotherapy composition and method		
INVENTOR(S):	Wiedmann, Tien-Wen Tao, Redwood City, CA, United States		
	Wang, Jian, Palo Alto, CA, United States		
	Pliam, Nathan B., Palo Alto, CA, United States		
	Wuh, Hank C. K., Los Altos, CA, United States		
PATENT ASSIGNEE(S):	Pharmagenesis, Inc., Palo Alto, CA, United States (U.S.		
	corporation)		
	NUMBER	DATE	
PATENT INFORMATION:	US 5843452	19981201	
APPLICATION INFO.:	US 1994-252953	19940602	(8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1992-973634, filed on 9 Nov 1992, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Rollins, John W.		

LEGAL REPRESENTATIVE: Dehlinger, Peter J.; Powers, Vincent M.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 1152
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 13 OF 21 USPATFULL
TI **Immunosuppressive drug** binding proteins and use
AB Purified **immunosuppressive drug** binding protein (immunophilin) of molecular weight 34-37 kDa and pI of about 6.5 is described. The 34-37 kDa immunophilin specifically binds FK-506, **rapamycin** and CsA with high affinity. This novel immunophilin can be used as a reagent for capturing, detecting and quantififying immunosuppressive drugs and their biologically active metabolites, derivatives and analogues in tissue or fluid samples, and for the capturing potential immunosuppressive drugs from microbial extracts or culture media.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:82604 USPATFULL
TITLE: **Immunosuppressive drug** binding proteins and use
INVENTOR(S): Soldin, Steven J., 6335 31st St., NW., Washington, DC, United States 20015

	NUMBER	DATE
PATENT INFORMATION:	US 5780307	19980714
APPLICATION INFO.:	US 1996-686759	19960726 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-200404, filed on 23 Feb 1994, now abandoned 76 Ser. No. US 1994-224868, filed on 8 Apr 1994 which is a continuation of Ser. No.
US -200404 which is a continuation-in-part of Ser. No. US 1991-782761, filed on 22 Oct 1991, now abandoned
And Ser. No. US 1992-841792, filed on 26 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-521074, filed on 9 May 1990, now abandoned , said Ser. No. US -782761 which is a continuation-in-part of Ser. No. US 1990-487115, filed on 2 Mar 1990, now abandoned which is a continuation-in-part of Ser. No. US 1988-279176, filed on 2 Dec 1988, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Stucker, Jeffrey
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 38 Drawing Figure(s); 34 Drawing Page(s)
LINE COUNT: 2374
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 14 OF 21 USPATFULL
TI Method for suppressing xenograft rejection
AB An improved method for suppressing xenograft rejection in a host subject is disclosed. The method includes administering an immunosuppressant drug, where the drug or the amount of drug administered is, by itself, ineffective to suppress xenograft rejection. Effective xenograft suppression is achieved by also administering an ethanolic extract of Triterygium wilfordii or a purified triptolide component thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:61170 USPATFULL
TITLE: Method for suppressing xenograft rejection
INVENTOR(S): [redacted]iedmann, Tien Wen Tao, Redwood [redacted]ty, CA, United States
Wang, Jian, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Pharmagenesis, Inc., Palo Alto, CA, United States (U.S.
corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5759550	19980602
APPLICATION INFO.:	US 1995-484782	19950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-307948, filed on 15 Sep 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-222853, filed on 5 Apr 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-58321, filed on 6 May 1993, now abandoned And a continuation-in-part of Ser. No. US 1994-252953, filed on 2 Jun 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Rollins, John W.
LEGAL REPRESENTATIVE: Powers, Vincent M.; Gorthey, LeeAnn
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Figure(s); 18 Drawing Page(s)
LINE COUNT: 1249
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 15 OF 21 USPATFULL
TI Methods and materials for the induction of T cell anergy
AB Anti-B7-1 antibodies or other B7-1 ligands may be used to prevent or treat a T-cell-mediated immune system disease in a patient or to induce antigen-specific tolerance.

The anti-B7-1 antibodies may be used to cause T cell anergy, treat allograft transplant rejection, treat graft versus host disease, and prevent or treat rheumatoid arthritis. An immunosuppressive agent is co-administered with the antibody.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:47964 USPATFULL
TITLE: Methods and materials for the induction of T cell anergy
INVENTOR(S): de Boer, Mark, Beverwijk, Netherlands
Conroy, Leah B., Pacifica, CA, United States
PATENT ASSIGNEE(S): Chiron Corporation, Emeryville, CA, United States (U.S.
corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5747034	19980505
APPLICATION INFO.:	US 1994-200716	19940218 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-15147, filed on 9 Feb 1993 which is a continuation-in-part of Ser. No. US 1992-910222, filed on 9 Jul 1992, now patented, Pat. No. US 5397703
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Loring, Susan A.
LEGAL REPRESENTATIVE: Pochopien, Donald J.; Savereide, Paul B.; Blackburn, Robert P.

NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2155
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 16 OF 21 USPATFULL
TI **Immunosuppressive drug** binding proteins and use
AB Purified **immunosuppressive drug** binding proteins (immunophilins) of molecular mass 2.4-3.0 kDa, 4.5 kDa, 34-37 kDa, 50-54 kDa, 80-100 kDa, and greater than about 120 kDa are described. The 34-37 kDa immunophilin specifically binds FK-506 and **rapamycin**. The 50-54 kDa immunophilin specifically binds FK-506, **rapamycin** and cyclosporine A, but with binding site distinctions. The 50-54 kDa immunophilin is devoid of significant rotomase activity, but inhibits cAMP-activated protein kinase activity. The amino acid composition, and the sequences of a dodecameric amino acid C-terminus partial sequence and of two heptameric internal partial amino acid sequences, of the 50-54 kDa immunophilin are described; the deduced molecular weight is 52,171. Recombinant about 52 kDa immunophilin is also described. These novel immunophilins can be used as reagents for the detection, quantification and capture of immunosuppressive drugs and their biologically active metabolites, derivatives and analogues in fluid samples, and for the capture of potential immunosuppressive drugs from microbial extracts or culture media or from mammalian body fluids and tissues.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:117940 USPATFULL
TITLE: **Immunosuppressive drug** binding proteins and use
INVENTOR(S): Soldin, Steven J., 6335 31st St., NW., Washington, DC, United States 20015

	NUMBER	DATE
PATENT INFORMATION:	US 5698448	19971216
APPLICATION INFO.:	US 1994-224868	19940408 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-200404, filed on 23 Feb 1994, now abandoned which is a continuation-in-part of Ser. No. US 1991-782761, filed on 22 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-487115, filed on 2 Mar 1990, now abandoned which is a continuation-in-part of Ser. No. US 1988-279176, filed on 2 Dec 1988, now abandoned , said Ser. No. US -200404 which is a continuation-in-part of Ser. No. US 1992-841792, filed on 26 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-521074, filed on 9 May 1990, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Nucker, Christine M.
ASSISTANT EXAMINER: Stucker, Jeffrey
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Figure(s); 31 Drawing Page(s)
LINE COUNT: 2277
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 17 OF 21 USPATFULL
TI Method for treating a LFA-1-mediated disorder

AB A method is provided for administering to a mammal suffering from, or at
risk for, a LFA[redacted]mediated disorder an initial d[redacted]ng of a therapeutically effective amount of LFA-1 antagonist, followed by a subsequent intermittent dosing of a therapeutically effective amount of LFA-1 antagonist that is less than 100%, calculated on a daily basis, of
the initial dosing of antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:33495 USPATFULL
TITLE:	Method for treating a LFA-1-mediated disorder
INVENTOR(S):	Jardieu, Paula M., Berkeley, CA, United States Montgomery, Bruce, Redwood City, CA, United States
PATENT ASSIGNEE(S):	Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5622700	19970422
APPLICATION INFO.:	US 1995-432543	19950502 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1994-287055, filed on 8 Aug 1994 which is a continuation of Ser. No. US 1993-128329, filed on 28 Sep 1993, now abandoned which is a continuation of Ser. No. US 1992-933269, filed on 21 Aug 1992, now abandoned	
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Chan, Christina Y.	
ASSISTANT EXAMINER:	Gambel, Phillip	
LEGAL REPRESENTATIVE:	Lee, Wendy M.	
NUMBER OF CLAIMS:	37	
EXEMPLARY CLAIM:	1,19	
NUMBER OF DRAWINGS:	11 Drawing Figure(s); 10 Drawing Page(s)	
LINE COUNT:	1757	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L17 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2001 ACS
TI New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation
AB We had previously shown that the drug undecylprodigiosin (UP) blocks human
lymphocyte proliferation in vitro. We have now investigated the mechanism
of action of a new analog of UP, PNU156804, which shows a more favorable activity profile than UP in mice. We demonstrate here that the biol. effect of PNU156804 in vitro is indistinguishable from UP: PNU156804 blocks human T **cell proliferation** in mid-late G1, as detd. by cell cycle anal., expression of cyclins, and cyclin-dependent kinases and retinoblastoma phosphorylation. In addn., we show that PNU156804 does not block significantly the induction of either IL-2 or IL-2R .alpha.- and .gamma.-chains but inhibits IL-2-dependent T **cell proliferation**. We have investigated several mol. pathways that are known to be activated by IL-2 in T cells. We show that PNU156804 does not inhibit c-myc and bcl-2 mRNA induction. On the other hand, PNU156804 efficiently inhibits the activation of the NF-KB and AP-1 transcription factors. PNU156804 inhibition of NF-KB activation is due to
the inhibition of the degrdn. of I.kappa.B-.alpha. and I.kappa.B-.beta.. PNU156804 action is restricted to some signaling pathways; it does not affect NF-KB activation by PMA in T cells but blocks that induced by CD40 crosslinking in B lymphocytes. We conclude that the prodigiosin family of

immunosuppressants is a new family of mols. that show a novel target specificity clearly distinct from that of other immunosuppressive drugs such as **cyclospor[redacted]A**, **FK506**, and **rapamycin**.

ACCESSION NUMBER: 1999:419178 HCAPLUS
DOCUMENT NUMBER: 131:165121
TITLE: New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation
AUTHOR(S): Mortellaro, Alessandra; Songia, Simona; Gnocchi, Paola; Ferrari, Mario; Fornasiero, Chiara; D'Alessio, Roberto; Isetta, Anna; Colotta, Francesco; Golay, Josee
CORPORATE SOURCE: Department of Immunology and Cell Biology, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy
SOURCE: J. Immunol. (1999), 162(12), 7102-7109
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 51
REFERENCE(S): (1) Abraham, R; Annu Rev Immunol 1996, V14, P483 HCAPLUS
(2) Ahmed, N; Proc Natl Acad Sci USA 1997, V94, P3627 HCAPLUS
(3) Ajchenbaum, F; J Biol Chem 1993, V268, P4113 HCAPLUS
(5) Baeuerle, P; Cell 1996, V87, P13 HCAPLUS
(6) Beadling, C; EMBO J 1994, V13, P5605 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2001 ACS
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**
AB The authors previously demonstrated the capacity of the hydroxylamine metabolite of sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. The authors studied the interaction of SMX-HA with the immunosuppressants **cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohemagglutinin, and phorbol myristate acetate and proliferation was detd. by cellular uptake of 3H-thymidine. Using median-effect anal. and concn. redn. index calcns. to assess **immunosuppressive drug** interactions, the authors produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concn. redns. at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, resp., were obsd. with 25 .mu.M SMX-HA, and this effect was not assocd. with reduced cell viability. SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concns. also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein prodn., which suggests that signaling events proximal to cytokine prodn. are not affected by the metabolite. Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.

ACCESSION NUMBER: 1997:271459 HCAPLUS
DOCUMENT NUMBER: 127:486
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**

AUTHOR(S): Hess, David A.; Bird, Ingrid A.; Almawi, Wassim Y.; Rieder, Michael J.

CORPORATE SOURCE: Dep. Paediatrics Pharmacol. To[redacted]ol. Robarts Res. Inst., Univ. Western Ontario, London, ON, Can.

SOURCE: J. Pharmacol. Exp. Ther. (1997), 281(1), 540-548
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

L17 ANSWER 20 OF 21 CA COPYRIGHT 2001 ACS

TI New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation

AB We had previously shown that the drug undecylprodigiosin (UP) blocks human lymphocyte proliferation in vitro. We have now investigated the mechanism of action of a new analog of UP, PNU156804, which shows a more favorable activity profile than UP in mice. We demonstrate here that the biol. effect of PNU156804 in vitro is indistinguishable from UP: PNU156804 blocks human T **cell proliferation** in mid-late G1, as detd. by cell cycle anal., expression of cyclins, and cyclin-dependent kinases and retinoblastoma phosphorylation. In addn., we show that PNU156804 does not block significantly the induction of either IL-2 or IL-2R .alpha.- and .gamma.-chains but inhibits IL-2-dependent T **cell proliferation**. We have investigated several mol. pathways that are known to be activated by IL-2 in T cells. We show that PNU156804 does not inhibit c-myc and bcl-2 mRNA induction. On the other hand, PNU156804 efficiently inhibits the activation of the NF-KB and AP-1 transcription factors. PNU156804 inhibition of NF-KB activation is due to the inhibition of the degrdn. of I.kappa.B-.alpha. and I.kappa.B-.beta.. PNU156804 action is restricted to some signaling pathways; it does not affect NF-KB activation by PMA in T cells but blocks that induced by CD40 crosslinking in B lymphocytes. We conclude that the prodigiosin family of immunosuppressants is a new family of mols. that show a novel target specificity clearly distinct from that of other immunosuppressive drugs such as **cyclosporin A**, **FK506**, and **rapamycin**.

ACCESSION NUMBER: 131:165121 CA

TITLE: New **immunosuppressive drug** PNU156804 blocks IL-2-dependent proliferation and NF-.kappa.B and AP-1 activation

AUTHOR(S): Mortellaro, Alessandra; Songia, Simona; Gnocchi, Paola; Ferrari, Mario; Fornasiero, Chiara; D'Alessio, Roberto; Isetta, Anna; Colotta, Francesco; Golay, Josee

CORPORATE SOURCE: Department of Immunology and Cell Biology, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy

SOURCE: J. Immunol. (1999), 162(12), 7102-7109
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 51

REFERENCE(S):
(1) Abraham, R; Annu Rev Immunol 1996, V14, P483 CA
(2) Ahmed, N; Proc Natl Acad Sci USA 1997, V94, P3627 CA
(3) Ajchenbaum, F; J Biol Chem 1993, V268, P4113 CA
(5) Baeuerle, P; Cell 1996, V87, P13 CAPLUS
(6) Beadling, C; EMBO J 1994, V13, P5605 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 21 OF 21 CA COPYRIGHT 2001 ACS
TI The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**
AB The authors previously demonstrated the capacity of the hydroxylamine metabolite of sulfamethoxazole (SMX-HA) to inhibit mitogen-induced T-**cell proliferation**. The authors studied the interaction of SMX-HA with the immunosuppressants **cyclosporin A** (CsA), **FK506** and **rapamycin**. Human peripheral blood mononuclear leukocytes were treated with SMX-HA and combined in culture with CsA or **FK506** or **rapamycin**. The cells were stimulated with phytohemagglutinin, and phorbol myristate acetate and proliferation was detd. by cellular uptake of 3H-thymidine. Using median-effect anal. and concn. redn. index calcns. to assess **immunosuppressive drug** interactions, the authors produced synergistic immunosuppression by SMX-HA/CsA and SMX-HA/**FK506**. Concn. redns. at the 50% inhibitory level of over 46-fold and 64-fold with CsA and **FK506**, resp., were obsd. with 25 .mu.M SMX-HA, and this effect was not assocd. with reduced cell viability. SMX-HA failed to augment the suppressive capacity of **rapamycin** in inhibiting mitogen-induced cellular proliferation. SMX-HA at immunosuppressive concns. also failed to interfere with interleukin-2 mRNA transcription and interleukin-2 protein prodn., which suggests that signaling events proximal to cytokine prodn. are not affected by the metabolite. Synergy between SMX-HA/**FK506** and SMX-HA/CsA suggests that the mechanism(s) of action of reactive sulfonamide metabolites may occur in later stages of lymphocyte activation.
ACCESSION NUMBER: 127:486 CA
TITLE: The hydroxylamine of sulfamethoxazole synergizes with **FK506** and **cyclosporin A**, inhibiting T-**cell proliferation**
AUTHOR(S): Hess, David A.; Bird, Ingrid A.; Almawi, Wassim Y.; Rieder, Michael J.
CORPORATE SOURCE: Dep. Paediatrics Pharmacol. Toxicol. Robarts Res. Inst., Univ. Western Ontario, London, ON, Can.
SOURCE: J. Pharmacol. Exp. Ther. (1997), 281(1), 540-548
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 10:36:05 ON 29 MAR 2001)

FILE 'MEDLINE, BIOSIS, BIOTECHDS, SCISEARCH, DGENE, EMBASE, USPATFULL, WPIDS, HCAPLUS, JAPIO, FSTA, JICST-EPLUS, FROSTI, CEN, CEABA-VTB, CA, BIOBUSINESS' ENTERED AT 10:37:06 ON 29 MAR 2001
L1 388590 S CELL PROLIFERATION
L2 6 S L1 AND (ACTIVATED BLOOD CELLS)
L3 0 S L1 AND (METHOD OF REVERSING PROLIFERATION?)
L4 102 S L1 AND (LACTACYSTIN)
L5 9 S L4 AND METHOD
L6 76319 S CYCLOSPORIN A
L7 14497 S RAPAMYCIN
L8 3147 S L7 AND L6
L9 18485 S FK506
L10 1471 S L8 AND L9
L11 83 S L10 AND IMMUNOSUPPRESSIVE DRUG
L12 57835 S PROTEASE INHIBITOR
L13 2614 S LACTACYSTIN

```
L14         2435 S PROTEASOME INHIBITOR
L15          787 S L13 AND L14
L16            0 S L15 AND L11
L17           21 S L11 AND L1
L18           30 S L15 AND L1
L19            0 S L17 AND L18

=> d l18 ti abs ibib tot


L18  ANSWER 1 OF 30  MEDLINE
TI   Delayed and sustained activation of p42/p44 mitogen-activated protein
     kinase induced by proteasome inhibitors through p21(ras) in PC12 cells.
AB   Proteolysis by the ubiquitin/proteasome pathway regulates the
     intracellular level of several proteins, some of which control
     cell proliferation and cell cycle progression. To
     determine what kinds of signaling cascades are activated or inhibited by
     proteasome inhibition, we treated PC12 cells with specific proteasome
     inhibitors and subsequently performed in-gel kinase assays.
     N-Acetyl-Leu-Leu-norleucinal and lactacystin, which inhibit the
     activity of the proteasome, induced the activation of p42/p44
     mitogen-activated protein (MAP) kinases [extracellular signal-regulated
     kinases (ERKs) 1 and 2]. In contrast, N-acetyl-Leu-Leu-methional, which
     inhibits the activity of calpains, but not of the proteasome, failed to
     induce ERK activation. Uniquely, the kinetics of MAP kinase activation
     induced by proteasome inhibitors are very slow compared with those
     resulting from activation by nerve growth factor; ERK activation is
     detectable only after a 5-h treatment with the inhibitors, and its
     activity remained unchanged for at least until 27 h. Proteasome
     inhibitor-initiated ERK activation is inhibited by pretreatment
     with the ERK kinase inhibitor PD 98059, as well as by overexpression of a
     dominant-negative form of Ras. Thus, proteasome inhibitors induce
     sustained ERK activation in a Ras-dependent manner. Proteasome
     inhibitor-induced neurite outgrowth, however, is not inhibited by
     PD 98059, indicating that sustained activation of ERKs is not the factor
     responsible for proteasome inhibitor-induced
     morphological differentiation. Our data suggest the presence of a novel
     mechanism for activation of the MAP kinase cascade that involves
     proteasome activity.
ACCESSION NUMBER:    2000083399     MEDLINE
DOCUMENT NUMBER:     20083399
TITLE:               Delayed and sustained activation of p42/p44
                     mitogen-activated protein kinase induced by proteasome
                     inhibitors through p21(ras) in PC12 cells.
AUTHOR:              Hashimoto K; Guroff G; Katagiri Y
CORPORATE SOURCE:    Section on Growth Factors, National Institute of Child
                     Health and Human Development, National Institutes of
                     Health, Bethesda, Maryland 20892, USA.
SOURCE:              JOURNAL OF NEUROCHEMISTRY, (2000 Jan) 74 (1) 92-8.
                     Journal code: JAV. ISSN: 0022-3042.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200003
ENTRY WEEK:          20000304

L18  ANSWER 2 OF 30  BIOSIS  COPYRIGHT 2001 BIOSIS
TI   Delayed and sustained activation of p42/p44 mitogen-activated protein
     kinase induced by proteasome inhibitors through p21ras in PC12 cells.
AB   Proteolysis by the ubiquitin/proteasome pathway regulates the
     intracellular level of several proteins, some of which control
     cell proliferation and cell cycle progression. To
     determine what kinds of signaling cascades are activated or inhibited by
```

proteasome inhibition, we treated PC12 cells with specific proteasome inhibitors and subsequently performed in-gel kinase assays. N-Acetyl-Leu-Leu-[redacted]leucinal and **lactacystin**, which inhibit the activity of the proteasome, induced the activation of p42/p44 mitogen-activated protein (MAP) kinases (extracellular signal-regulated kinases (ERKs) 1 and 2). In contrast, N-acetyl-Leu-Leu-methional, which inhibits the activity of calpains, but not of the proteasome, failed to induce ERK activation. Uniquely, the kinetics of MAP kinase activation induced by proteasome inhibitors are very slow compared with those resulting from activation by nerve growth factor; ERK activation is detectable only after a 5-h treatment with the inhibitors, and its activity remained unchanged for at least until 27 h. **Proteasome inhibitor**-initiated ERK activation is inhibited by pretreatment with the ERK kinase inhibitor PD 98059, as well as by overexpression of a dominant-negative form of Ras. Thus, proteasome inhibitors induce sustained ERK activation in a Ras-dependent manner. **Proteasome inhibitor**-induced neurite outgrowth, however, is not inhibited by PD 98059, indicating that sustained activation of ERKs is not the factor responsible for **proteasome inhibitor**-induced morphological differentiation. Our data suggest the presence of a novel mechanism for activation of the MAP kinase cascade that involves proteasome activity.

ACCESSION NUMBER: 2000:87658 BIOSIS
DOCUMENT NUMBER: PREV200000087658
TITLE: Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21ras in PC12 cells.
AUTHOR(S): Hashimoto, Keiko; Guroff, Gordon; Katagiri, Yasuhiro (1)
CORPORATE SOURCE: (1) Section on Growth Factors, National Institute of Child Health and Human Development, National Institutes of Health, 9000 Rockville Pike, Building 49, Room 5A51, Bethesda, MD, 20892 USA
SOURCE: Journal of Neurochemistry, (Jan., 2000) Vol. 74, No. 1, pp. 92-98.
ISSN: 0022-3042.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 3 OF 30 BIOSIS COPYRIGHT 2001 BIOSIS
TI Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AB Vascular smooth muscle cells exhibit a striking plasticity and are able to change from a differentiated, contractile phenotype to a more immature, synthetic phenotype. This includes a prominent structural reorganization with loss of myofilaments and construction of a large secretory apparatus.
As a result, the cells lose their contractility and become able to migrate, proliferate, and secrete extracellular matrix components. In vivo, this phenotypic shift is a chief factor behind the involvement of smooth muscle cells in formation of atherosclerotic and restenotic lesions. Here, the effects of the proteasome inhibitors carbobenzoxy-leucyl-leucyl-leucinal, N-acetyl-leucyl-leucyl-norleucinal, and **lactacystin** on the morphologic structure and growth of rat aortic smooth muscle cells in primary culture were examined. Electron microscopic analysis revealed that the volume density of myofilaments was higher and the volume density of the endoplasmic reticulum and the Golgi complex was lower incells exposed to these drugs than in solvent-treated controls. Moreover, diffuse material representing incompletely degraded proteins gathered in the cytoplasm of exposed cells. Similar material was also found in lysosomes. Immunogold staining showed a positive reaction in

the diffuse cytoplasmic aggregates with antibodies against ubiquitin-protein conjugates and proteasomes, whereas the material collecting in lysosomes reacted only with those against ubiquitin-protein conjugates. Moreover, weak staining for smooth muscle alpha-actin was noted in the cytoplasmic aggregates. Otherwise, reactivity for this protein was concentrated in myofilaments. In addition to the effects on cell structure described above, the proteasome inhibitors blocked cell multiplication. This was probably due to a decreased rate of transition into a synthetic state as well as direct interference with cell cycle progression in synthetic cells. These observations suggest that proteasomes have the major responsibilityfor protein degradation during transition of smooth muscle cells from a contractile to a synthetic phenotype. If proteasome activity is inhibited, undegraded material accumulates in the cytoplasm and is only partially taken up into lysosomes for digestion. These findings raise the possibility that proteasome inhibitors may have a beneficial effect on vascular pathologies associated with phenotypic modulation and proliferation of smooth muscle cells.

ACCESSION NUMBER: 1999:510184 BIOSIS
DOCUMENT NUMBER: PREV199900510184
TITLE: Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AUTHOR(S): Thyberg, Johan (1); Blomgren, Karin
CORPORATE SOURCE: (1) Department of Cell and Molecular Biology, Karolinska Institut, S-171 77, Stockholm Sweden
SOURCE: Laboratory Investigation, (Sept., 1999) Vol. 79, No. 9, pp. 1077-1088.
ISSN: 0023-6837.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 4 OF 30 SCISEARCH COPYRIGHT 2001 ISI (R)
TI Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21(ras) in PC12
AB Proteolysis by the ubiquitin/proteasome pathway regulates the intracellular level of several proteins, some of which control **cell proliferation** and cell cycle progression. To determine what kinds of signaling cascades are activated or inhibited by proteasome inhibition, we treated PC12 cells with specific proteasome inhibitors and subsequently performed in-gel kinase assays. N-Acetyl-Leu-Leu-norleucinal and **lactacystin**, which inhibit the activity of the proteasome, induced the activation of p42/p44 mitogen-activated protein (MAP) kinases [extracellular signal-regulated kinases (ERKs) 1 and 2], In contrast, N-acetyl-Leu-Leu-methional, which inhibits the activity of calpains, but not of the proteasome, failed to induce ERK activation. Uniquely, the kinetics of MAP kinase activation induced by proteasome inhibitors are very slow compared with those resulting from activation by nerve growth factor; ERK activation is detectable only after a 5-h treatment with the inhibitors, and its activity remained unchanged for at least until 27 h. **Proteasome inhibitor**-initiated ERK activation is inhibited by pretreatment with the ERK kinase inhibitor PD 98059, as well as by overexpression of a dominant-negative form of Pas. Thus, proteasome inhibitors induce sustained ERK activation in a Pas-dependent manner. **Proteasome inhibitor**-induced neurite outgrowth, however, is not inhibited by PD 98059, indicating that sustained activation of ERKs is not the factor responsible for **proteasome inhibitor**-induced morphological differentiation. Our data suggest the presence of a novel mechanism for activation of the MAP kinase cascade that involves proteasome activity.

ACCESSION NUMBER: 2000:3792 SCISEARCH
THE GENUINE ARTICLE: 266HM
TITLE: D[redacted]yed and sustained activation o[redacted]42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21(ras) in PC12
AUTHOR: Hashimoto K; Guroff G; Katagiri Y (Reprint)
CORPORATE SOURCE: NICHHD, GROWTH FACTORS SECT, NIH, BLDG 49, ROOM 5A51, 9000
ROCKVILLE PIKE, BETHESDA, MD 20892 (Reprint); NICHHD, GROWTH FACTORS SECT, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NEUROCHEMISTRY, (JAN 2000) Vol. 74, No. 1, pp. 92-98.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621.
ISSN: 0022-3042.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 5 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Proteasome inhibitors induce caspase-dependent apoptosis and accumulation of p21(WAF1/Cip1) in human immature leukemic cells.
AB The 26S proteasome is a non-lysosomal multicatalytic protease complex for degrading intracellular proteins by ATP/ubiquitin-dependent proteolysis. Tightly ordered proteasomal degradation of proteins critical for cell cycle control implies a role of the proteasome in maintaining **cell proliferation** and cell survival. In this study, we demonstrate that cell-permeable proteasome inhibitors, **lactacystin**, benzyloxycarbonyl(Z)-leucyl-leucyl-leucinal (ZLLLal; MG-132) and 4-hydroxy-5-iodo-3-nitrophenylacetyl-leucyl-leucyl-leucine vinyl sulfone (NLVS), induce apoptosis abundantly in p53-defective leukemic cell lines CCRF-CEM, U937 and K562 as well as in myelogenic and lymphatic leukemic cells obtained from adult individuals with relapsed acute leukemias. Leukemic cell apoptosis induced by the proteasome inhibitors was dependent on activation of caspase-3 and related caspase family proteases, because caspase-3 inhibitor N-acetyl-L-aspartyl-L-glutamyl-L-valyl-L-aspartal (Ac-DEVD-cho) and, more effectively, the general caspase-inhibitor N-benzyloxycarbonyl-L-valyl-L-alanyl-L-aspartate fluoromethylketone (Z-VAD-fmk) were capable of blocking apoptosis induced by **lactacystin**, ZLLLal or NLVS. Induction of apoptosis by **lactacystin** or ZLLLal was accompanied by cell cycle arrest at G2/M phase and by accumulation and stabilization of cyclin-dependent kinase (WAF1/Cip) inhibitor p21 and tumor suppressor protein p53. A role of p53 in mediating apoptosis or induction of p21(WAF1/Cip1) was ruled out since CCRF-CEM and U937 cells express non-functional mutant p53, and K562 cells lack expression of p53. Viability and hematopoietic outgrowth of human CD34+ progenitor cells treated with **lactacystin** were slightly reduced, whereas treatment of CD34+ cells with ZLLLal or the cytostatic drugs doxorubicin and gemcitabine resulted in markedly reduced viability and hematopoietic outgrowth. These results demonstrate a basic role of the proteasome in maintaining survival of human leukemic cells, and may define cell-permeable proteasome inhibitors as potently anti-leukemic agents which exhibit a moderate hematopoietic toxicity in vitro.
ACCESSION NUMBER: 2000358614 EMBASE
TITLE: Proteasome inhibitors induce caspase-dependent apoptosis and accumulation of p21(WAF1/Cip1) in human immature leukemic cells.
AUTHOR: Naujokat C.; Sezer O.; Zinke H.; Leclere A.; Hauptmann S.;

Possinger K.
CORPORATE SOURCE: C. Naujokat, Institut fur Immunologie, Ruprecht-Karls-Univ. Heidelberg, Im Neuenheimer Feld 305, D-69120 Heidelberg, Germany. cord.naujokat@urz.uni-heidelberg.de
SOURCE: European Journal of Haematology, (2000) 65/4 (221-236).
Refs: 65
ISSN: 0902-4441 CODEN: EJHAEC
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 6 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Proteasome inhibitors as anti-cancer agents.
AB The ubiquitin (Ub)-proteasome pathway is the major non-lysosomal pathway of proteolysis in human cells and accounts for the degradation of most short-lived, misfolded or damaged proteins. This pathway is important in the regulation of a number of key biological regulatory mechanisms. Proteins are usually targeted for proteasome-mediated degradation by polyubiquitinylation, the covalent addition of multiple units of the 76 amino acid protein Ub, which are ligated to .epsilon.-amino groups of lysine residues in the substrate. Polyubiquitinylated proteins are degraded by the 26S proteasome, a large, ATP-dependent multicatalytic protease complex, which also regenerates monomeric Ub. The targets of this pathway include key regulators of **cell proliferation** and cell death. An alternative form of the proteasome, termed the immunoproteasome, also has important functions in the generation of peptides for presentation by MHC class I molecules. In recent years there has been a great deal of interest in the possibility that proteasome inhibitors, through elevation of the levels of proteasome targets, might prove useful as a novel class of anti-cancer drugs. Here we review the progress made to date in this area and highlight the potential advantages and weaknesses of this approach. (C) 2000 Lippincott Williams and Wilkins.
ACCESSION NUMBER: 2000315015 EMBASE
TITLE: Proteasome inhibitors as anti-cancer agents.
AUTHOR: Murray R.Z.; Norbury C.
CORPORATE SOURCE: C. Norbury, Imp. Can. Res. Fund Mol. Oncol. Lab., Univ. of Oxford Inst. of Molec. Med., John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom. norbury@icrf.icnet.uk
SOURCE: Anti-Cancer Drugs, (2000) 11/6 (407-417).
Refs: 110
ISSN: 0959-4973 CODEN: ANTDEV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 7 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI p53 Stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14(APF)-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells.
AB Human T-cell lymphotropic virus type I (HTLV-I) transforms T cells in vitro, and the viral transactivator Tax functionally impairs the tumor

suppressor p53 protein, which is also stabilized in HTLV-I-infected T cells. Thus, the functional impairment of p53 is essential to maintain the viral- induced proliferation of CD4+ mature T cells. However, in the CD4+ leukemic cells of patients with adult T-cell leukemia/lymphoma (ATLL), the viral transactivator does not appear to be expressed, and p53 mutations have been found only in a fraction of patients. We sought to investigate whether p53 function is impaired, in ex vivo samples from patients with ATLL, in the absence of genetic mutations. Here we demonstrate that the p53 protein is stabilized also in ex vivo ATLL samples (10 of 10 studied) and that at least in 2 patients p53 stabilization was not associated with genetic mutation. Furthermore, the assessment of p53 function after ionizing radiation of ATLL cells indicated an abnormal induction of the p53-responsive genes GADD45 and p21(WAF1) in 7 of 7 patients. In 2 of 2 patients, p53 regulation of cell- cycle progression appeared to be impaired as well. Because p53 is part of a regulatory loop that also involves MDM2 and p14(ARF), the status of the latter proteins was also assessed in cultured or fresh ATLL cells. The p97 MDM2 protein was not detected by Western blot analysis in established HTLV-I- infected T-cell lines or ex vivo ATLL cell lysates. However, the MDM2 protein could be easily detected after treatment of cells with the specific **proteasome inhibitor lactacystin**, suggesting a normal regulation of the p53- MDM2 regulating loop. Similarly, p14(ARF) did not appear to be aberrantly expressed in ex vivo ATLL cells nor in any of the established HTLV-I-infected T-cell lines studied. Thus, p53 stabilization in HTLV-I infection occurs in the absence of genetic mutation and alteration of the physiologic degradation pathway of p53. (C) 2000 by The American Society of Hematology.

ACCESSION NUMBER: 2000222670 EMBASE
TITLE: p53 Stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14(APF)-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells.
AUTHOR: Takemoto S.; Trovato R.; Cereseto A.; Nicot C.; Kislyakova T.; Casareto L.; Waldmann T.; Torelli G.; Franchini G.
CORPORATE SOURCE: G. Franchini, 41/0804 Basic Research Laboratory, Division of Basic Sciences, National Cancer Institute, Bethesda, MD 20892, United States
SOURCE: Blood, (15 Jun 2000) 95/12 (3939-3944).
Refs: 37
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 8 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI The selective proteasome inhibitors **lactacystin** and epoxomicin can be used to either up- or down-regulate antigen presentation at nontoxic doses.
AB The complete inhibition of proteasome activities interferes with the production of most MHC class I peptide ligands as well as with cellular proliferation and survival. In this study we have investigated how partial and selective inhibition of the chymotrypsin-like activity of the proteasome by the proteasome inhibitors **lactacystin** or epoxomicin would affect Ag presentation. At 0.5-1 .mu.M **lactacystin**, the presentation of the lymphocytic choriomeningitis

virus-derived epitopes NP118 and GP33 and the mouse CMV epitope pp89-168 were reduced and were further diminished in a dose-dependent manner with increasing concentrations. Presentation of the lymphocytic choriomeningitis virus-derived epitope GP276, in contrast, was markedly enhanced at low, but abrogated at higher, concentrations of either **lactacystin** or epoxomicin. The inhibitor-mediated effects were thus epitope specific and did not correlate with the degradation rates of the involved viral proteins. Although neither apoptosis induction nor interference with cellular proliferation was observed at 0.5-1 .mu.M **lactacystin** in vivo, this concentration was sufficient to alter the fragmentation of polypeptides by the 20S proteasome in vitro. Our results indicate that partial and selective inhibition of proteasome activity in vivo is a valid approach to modulate Ag presentation, with potential applications for the treatment of autoimmune diseases and the prevention of transplant rejection.

ACCESSION NUMBER: 2000219889 EMBASE
TITLE: The selective proteasome inhibitors **lactacystin** and epoxomicin can be used to either up- or down-regulate antigen presentation at nontoxic doses.
AUTHOR: Schwarz K.; De Giuli R.; Schmidtke G.; Kostka S.; Van den Broek M.; Kyung Bo Kim; Crews C.M.; Kraft R.; Groettrup M.
CORPORATE SOURCE: Dr. M. Groettrup, Kantonsspital St. Gallen, Laborforschungsabteilung, Haus 09, CH-9007 St. Gallen, Switzerland. lfal@msl.kssg.ch
SOURCE: Journal of Immunology, (15 Jun 2000) 164/12 (6147-6157). Refs: 52
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 9 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI **Proteasome inhibitor** induced gene expression profiles reveal overexpression of transcriptional regulators ATF3, GADD153 and MAD1.
AB The ubiquitin/proteasome pathway has been implicated in a wide variety of cellular processes and the number of substrates degraded by the proteasome is impressive. Most prominently, the stability of a large number of transcription factors is regulated by ubiquitination. To elucidate pathways regulated by the proteasome, gene expression profiles were generated, comparing changes of mRNA expression of 7900 genes from the UniGene collection upon exposure of cells to the proteasome inhibitors **Lactacystin**, **Lactacystin**-.beta.-lactone or MG132 by means of microarray based cDNA hybridization. The three profiles were very similar, but differed significantly from a gene expression profile generated with the histone deacetylase inhibitor Trapoxin A, indicating that the observed alterations were indeed due to proteasome inhibition. Two of the most prominently induced genes encoded the growth arrest and DNA damage inducible protein Gadd153 and the activating transcription factor ATF3, both transcription factors of the CCAAT/enhancer binding protein (C/EBP) family. A third gene encoded for the transcriptional repressor and c-Myc antagonist Mad1. Our results suggest that proteasome inhibition leads to upregulation of specific members of transcription factor families controlling cellular stress response and proliferation.
ACCESSION NUMBER: 2000210491 EMBASE
TITLE: **Proteasome inhibitor** induced gene expression profiles reveal overexpression of transcriptional regulators ATF3, GADD153 and MAD1.
AUTHOR: Zimmermann J.; Erdmann D.; Lalande I.; Grossenbacher R.;

Noorani M.; Furst P.
CORPORATE SOURCE: P. Furst, Novartis Pharma AG, Oncology Research, WK[redacted]25.13.14, CH-4002 Basel, Switz[redacted]and
SOURCE: Oncogene, (8 Jun 2000) 19/25 (2913-2920).
Refs: 52
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 10 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI p27(Kip1) Accumulation by inhibition of proteasome function induces apoptosis in oral squamous cell carcinoma cells.
AB Ubiquitin-mediated proteolysis controls intracellular levels of various cell cycle regulatory proteins, and its inhibition has been shown to induce apoptosis in proliferating cells. In the present study, we examined induction of apoptosis in oral squamous cell carcinoma (OSCC) cells by treatment with specific proteasome inhibitors, carbobenzoxy-L-leucyl-L-leucyl-L-norvalinal and **lactacystin**. In all three OSCC cell lines examined, apoptotic changes such as apoptotic body formation and DNA fragmentation were observed at various degrees after 24 h of the carbobenzoxy-L-leucyl-L-leucyl-L-norvalinal or **lactacystin** treatment. HSC2 cells showed the most prominent apoptotic changes among the cell lines examined and demonstrated the highest level of accumulation of p27(Kip1) protein after the treatment with **proteasome inhibitor**. Reduced expressions of cyclin D1 and phospho pRb were also observed after the treatment with **proteasome inhibitor**. Moreover, 12 h of treatment with the **proteasome inhibitor** inhibited cdk2/cyclin E kinase activity and increased the ratio of the cell cycle population at the G1 phase. The **proteasome inhibitor** led to inhibition of cell cycle progression. In addition, activation of CPP32 and reduced expression of Bcl-2 were observed. Because apoptosis induced by the **proteasome inhibitor** was inhibited by treatment with antisense p27(Kip1) oligonucleotide, accumulation of the p27(Kip1) protein might play an important role in the apoptosis induced by **proteasome inhibitor**. The present results suggest that inhibition of proteasome function may be used as a possible target of novel therapy for OSCC.
ACCESSION NUMBER: 2000106908 EMBASE
TITLE: p27(Kip1) Accumulation by inhibition of proteasome function induces apoptosis in oral squamous cell carcinoma cells.
AUTHOR: Kudo Y.; Takata T.; Ogawa I.; Kaneda T.; Sato S.; Takekoshi T.; Zhao M.; Miyauchi M.; Nikai H.
CORPORATE SOURCE: Y. Kudo, Department of Oral Pathology, Hiroshima University, Faculty of Dentistry, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan
SOURCE: Clinical Cancer Research, (2000) 6/3 (916-923).
Refs: 47
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

L18 ANSWER 11 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21(ras) in PC 12 cells.
AB Proteolysis by the ubiquitin/proteasome pathway regulates the intracellular level of several proteins, some of which control **cell proliferation** and cell cycle progression. To determine what kinds of signaling cascades are activated-or inhibited by proteasome inhibition, we treated PC12 cells with specific proteasome inhibitors and subsequently performed in-gel kinase assays. N-Acetyl-Leu-Leu-norleucinal and **lactacystin**, which inhibit the activity of the proteasome, induced the activation of p42/p44 mitogen-activated protein (MAP) kinases [extracellular signal- regulated kinases (ERKs) 1 and 2]. In contrast, N-acetyl-Leu-Leu-methional, which inhibits the activity of calpains, but not of the proteasome, failed to induce ERK activation. Uniquely, the kinetics of MAP kinase activation induced by proteasome inhibitors are very slow compared with those resulting from activation by nerve growth factor; ERK activation is detectable only after a 5-h treatment with the inhibitors, and its activity remained unchanged for at least until 27 h. **Proteasome inhibitor**-initiated ERK activation is inhibited by pretreatment with the ERK kinase inhibitor PD 98059, as well as by overexpression of a dominant-negative form of Ras. Thus, proteasome inhibitors induce sustained ERK activation in a Ras-dependent manner. **Proteasome inhibitor**-induced neurite outgrowth, however, is not inhibited by PD 98059, indicating that sustained activation of ERKs is not the factor responsible for **proteasome inhibitor**-induced morphological differentiation. Our data suggest the presence of a novel mechanism for activation of the MAP kinase cascade that involves proteasome activity.
ACCESSION NUMBER: 2000008955 EMBASE
TITLE: Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21(ras) in PC 12 cells.
AUTHOR: Hashimoto K.; Guroff G.; Katagiri Y.
CORPORATE SOURCE: Dr. Y. Katagiri, Section on Growth Factors, Child Hlth. Natl. Inst./Human Devt., National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, United States. katagiri@box-k.nih.gov
SOURCE: Journal of Neurochemistry, (2000) 74/1 (92-98). Refs: 41 ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 12 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AB Vascular smooth muscle cells exhibit a striking plasticity and are able to change from a differentiated, contractile phenotype to a more immature, synthetic phenotype. This includes a prominent structural reorganization with loss of myofilaments and construction of a large secretory apparatus. As a result, the cells lose their contractility and become able to migrate, proliferate, and secrete extracellular matrix components. In vivo, this phenotypic shift is a chief factor behind the involvement of smooth muscle cells in formation of atherosclerotic and restenotic lesions. Here, the effects of the proteasome inhibitors

carbobenzoxy-leucyl-leucyl-leucinal, N- acetyl-leucyl-leucyl-norleucinal, and **lactacystin** on the morphologic structure and growth of rat aortic smooth muscle cells in primary culture were examined. Electron microscopic analysis revealed that the volume density of myofilaments was higher and the volume density of the endoplasmic reticulum and the Golgi complex was lower in cells exposed to these drugs than in solvent-treated controls. Moreover, diffuse material representing incompletely degraded proteins gathered in the cytoplasm of exposed cells. Similar material was also found in lysosomes. Immunogold staining showed a positive reaction in the diffuse cytoplasmic aggregates with antibodies against ubiquitin-protein conjugates and proteasomes, whereas the material collecting in lysosomes reacted only with those against ubiquitin-protein conjugates. Moreover, weak staining for smooth muscle .alpha.-actin was noted in the cytoplasmic aggregates. Otherwise, reactivity for this protein was concentrated in myofilaments. In addition to the effects on cell structure described above, the proteasome inhibitors blocked cell multiplication. This was probably due to a decreased rate of transition into a synthetic state as well as direct interference with cell cycle progression in synthetic cells. These observations suggest that proteasomes have the major responsibility for protein degradation during transition of smooth muscle cells from a contractile to a synthetic phenotype. If proteasome activity is inhibited, undegraded material accumulates in the cytoplasm and is only partially taken up into lysosomes for digestion. These findings raise the possibility that proteasome inhibitors may have a beneficial effect on vascular pathologies associated with phenotypic modulation and proliferation of smooth muscle cells.

ACCESSION NUMBER: 1999329631 EMBASE
TITLE: Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture.
AUTHOR: Thyberg J.; Blomgren K.
CORPORATE SOURCE: Dr. J. Thyberg, Department of Cell/Molecular Biology, Karolinska Institut, Box 285, S-171 77 Stockholm, Sweden. Johan.Thyberg@cmb.ki.se
SOURCE: Laboratory Investigation, (1999) 79/9 (1077-1088). Refs: 42
ISSN: 0023-6837 CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 13 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-CoA reductase.
AB In this paper we present the finding that lovastatin arrests cells by inhibiting the proteasome, which results in the accumulation of p21 and p27, leading to G1 arrest. Lovastatin is an inhibitor of hydroxymethyl glutaryl (HMG)-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Previously, we reported that lovastatin can be used to arrest cultured cells in the G1 phase of the cell cycle, resulting in the stabilization of the cyclin-dependent kinase inhibitors (CKIs) p21 and p27. In this report we show that this stabilization of p21 and p27 may be the result of a previously unknown function of the pro-drug, .beta.-lactone ring form of lovastatin to inhibit the proteasome degradation of these CKIs. The lovastatin mixture used in this study is 80% open-ring form and 20% pro-drug, .beta.-lactone form. We show that while the lovastatin open-ring form and pravastatin (a lovastatin

analogue, 100% open ring) inhibit the HMG-CoA reductase enzyme, lovastatin
pro-drug inhibits the proteasome but does not inhibit HMG-CoA reductase. In addition, many of the properties of proteasome inhibition by the prodrug are the same as the specific **proteasome inhibitor lactacystin**. Lastly, mevalonate (used to rescue cells from lovastatin arrest) unexpectedly abrogates the **lactacystin** and lovastatin pro-drug inhibition of the proteasome. Mevalonate increases the activity of the proteasome, which results in degradation of the CKIs, allowing lovastatin- and **lactacystin** -arrested cells to resume cell division. The lovastatin-mediated inhibition of the proteasome suggests a unique mechanism for the chemopreventative effects of this agent seen in human cancer.

ACCESSION NUMBER: 1999246273 EMBASE
TITLE: Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-CoA reductase.
AUTHOR: Rao S.; Porter D.C.; Chen X.; Herliczek T.; Lowe M.; Keyomarsi K.
CORPORATE SOURCE: K. Keyomarsi, Wadsworth Center, Empire State Plaza, P.O. Box 509, Albany, NY 12201-0509, United States. keyomars@wadsworth.org
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (6 Jul 1999) 96/14 (7797-7802). Refs: 40
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L18 ANSWER 14 OF 30 USPATFULL
TI **Lactacystin** analogs
AB Compounds related to **lactacystin** and **lactacystin** .beta.-lactone, pharmaceutical compositions containing the compounds, and methods of use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:153855 USPATFULL
TITLE: **Lactacystin** analogs
INVENTOR(S): Fenteany, Gabriel, Cambridge, MA, United States
Jamison, Timothy F., Cambridge, MA, United States
Schreiber, Stuart L., Boston, MA, United States
Standaert, Robert F., Arlington, MA, United States
PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6147223	20001114
APPLICATION INFO.:	US 1995-468408	19950606 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-421583, filed on 12 Apr 1995
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Gerstl, Robert
LEGAL REPRESENTATIVE: Hale and Dorr LLP
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 15 OF 30 USPATFULL

TI Inhibition of 26S and 20S proteasome by indanones
AB This invention is novel indanone compositions useful for inhibiting **cell proliferati** disorders in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:121530 USPATFULL
TITLE:	Inhibition of 26S and 20S proteasome by indanones
INVENTOR(S):	Lum, Robert T., Palo Alto, CA, United States Schow, Steven R., Redwood City, CA, United States Joly, Alison, San Mateo, CA, United States Kerwar, Suresh, Westchester, NY, United States Nelson, Marek G., Sunol, CA, United States Wick, Michael M., Chestnut Hill, MA, United States
PATENT ASSIGNEE(S):	CV Therapeutics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6117887	20000912
APPLICATION INFO.:	US 1998-88581	19980602 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1996-719042, filed on 24 Sep 1996, now patented, Pat. No. US 5834487	
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Reamer, James H.	
LEGAL REPRESENTATIVE:	McDonnell Boehnen Hulbert & Berghoff	
NUMBER OF CLAIMS:	9	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)	
LINE COUNT:	976	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 16 OF 30 USPATFULL
TI .alpha.-ketoamide inhibitors of 20S proteasome
AB .alpha.-ketoamide compounds useful for treating disorders mediated by 20S proteasome in mammals having the following formula: wherein X.sub.2 is Ar or Ar--X.sub.3 wherein X.sub.3 is --C.dbd.O, or --CH.sub.2 CO--, and wherein Ar is phenyl, substituted phenyl, indole, substituted indoles, and any other heteroaryls; R.sub.1, and R.sub.2 are each individually selected from the side chains of the known natural .alpha.-amino acids and unnatural amino acids, hydrogen, 1-10 carbon linear and branched alkyl, 1-10 carbon linear and branched substituted alkyl, aryl, substituted aryl, 1-10 carbon linear, branched substituted aryl, alkoxyaryl, 3-8 carbon cycloalkyl, heterocycle substituted heterocycle, heteroaryl and substituted heteroaryl; X.sub.1 is selected from hydroxide, monoalkylamino, dialkylamino, alkoxide, arylkoxide and ##STR1## wherein X.sub.4 is hydroxide, arylamino, monoalkylamino, dialkylamino, alkoxide, or arylalkoxide; and R.sub.3 is selected from the known natural .alpha.-amino acids, unnatural amino acids, hydrogen, 1-10 carbon linear and branched alkyl, 1-10 carbon linear and branched substituted alkyl, aryl, substituted aryl, 1-10 carbon linear and branched substituted aryl, alkoxyaryl, 3-8 carbon cycloalkyl, heterocycle, substituted heterocycle, heteroaryl and substituted heteroaryl.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:74414 USPATFULL
TITLE:	.alpha.-ketoamide inhibitors of 20S proteasome
INVENTOR(S):	Wang, Lisa, Burlingame, CA, United States Lum, Robert T., Palo Alto, CA, United States Schow, Steven R., Redwood City, CA, United States Joly, Alison, San Mateo, CA, United States Kerwar, Suresh, Westchester, NY, United States Wick, Michael M, Chestnut Hill, MA, United States
PATENT ASSIGNEE(S):	CV Therapeutics, Inc., Palo Alto, CA, United States

(U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 6075150	20000613	
APPLICATION INFO.:	US 1998-13365	19980126	(9)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Davis, Brian J.
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 1523
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 17 OF 30 USPATFULL
TI Inhibition of 26S and 20S proteasome by indanones
AB This invention is a method for inhibiting **cell proliferation** using indanones.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:138919 USPATFULL
TITLE: Inhibition of 26S and 20S proteasome by indanones
INVENTOR(S): Lum, Robert T., Palo Alto, CA, United States
Schow, Steven R., Redwood City, CA, United States
Joly, Alison, San Mateo, CA, United States
Kerwar, Suresh, Westchester, NY, United States
Nelson, Marek G., Sunol, CA, United States
Wick, Michael M., Chestnut Hill, MA, United States
PATENT ASSIGNEE(S): CV Therapeutics, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5834487	19981110	
APPLICATION INFO.:	US 1996-719042	19960924	(8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: McDonnell Boehnen Hulbert & Berghoff
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1104
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 18 OF 30 USPATFULL
TI **Lactacystin** analogs
AB Described herein are compounds related to **lactacystin** and **lactacystin** .beta.-lactone, pharmaceutical compositions containing the compounds, and methods of use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:58182 USPATFULL
TITLE: **Lactacystin** analogs
INVENTOR(S): Fenteany, Gabriel, Cambridge, MA, United States
Jamison, Timothy F., Cambridge, MA, United States
Schreiber, Stuart L., Boston, MA, United States
Standaert, Robert F., Arlington, MA, United States
PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5756764	19980526

APPLICATION INFO.: US 1995-466468 19950606 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1995-421583, filed on 12 Apr 1995
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Stockton, Laura L.
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 2392
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L18 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI p53 stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14ARF-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells
AB Human T-cell lymphotropic virus type I (HTLV-I) transforms T cells in vitro, and the viral transactivator Tax functionally impairs the tumor suppressor p53 protein, which is also stabilized in HTLV-I-infected T cells. Thus, the functional impairment of p53 is essential to maintain the viral-induced proliferation of CD4+ mature T cells. However, in the CD4+ leukemic cells of patients with adult T-cell leukemia/lymphoma (ATLL), the viral transactivator does not appear to be expressed, and p53 mutations have been found only in a fraction of patients. We sought to investigate whether p53 function is impaired, in ex vivo samples from patients with ATLL, in the absence of genetic mutations. Here we demonstrate that the p53 protein is stabilized also in ex vivo ATLL samples (10 of 10 studied) and that at least in 2 patients p53 stabilization was not assocd. with genetic mutation. Furthermore, the assessment of p53 function after ionizing radiation of ATLL cells indicated an abnormal induction of the p53-responsive genes GADD45 and p21WAF1 in 7 of 7 patients. In 2 of 2 patients, p53 regulation of cell-cycle progression appeared to be impaired as well. Because p53 is part of a regulatory loop that also involves MDM2 and p14ARF, the status of the latter proteins was also assessed in cultured or fresh ATLL cells. The p97 MDM2 protein was not detected by Western blot anal. in established HTLV-I-infected T-cell lines or ex vivo ATLL cell lysates. However, the MDM2 protein could be easily detected after treatment of cells with the specific **proteasome inhibitor lactacystin**, suggesting a normal regulation of the p53-MDM2 regulating loop. Similarly, p14ARF did not appear to be aberrantly expressed in ex vivo ATLL cells nor in any of the established HTLV-I-infected T-cell lines studied. Thus, p53 stabilization in HTLV-I infection occurs in the absence of genetic mutation and alteration of the physiol. degrdn. pathway of p53.
ACCESSION NUMBER: 2000:414259 HCAPLUS
DOCUMENT NUMBER: 133:133279
TITLE: p53 stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14ARF-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells
AUTHOR(S): Takemoto, Shigeki; Trovato, Raffaella; Cereseto, Anna; Nicot, Christophe; Kislyakova, Tatiana; Casareto, Luca; Waldmann, Thomas; Torelli, Giuseppe; Franchini, Genoveffa
CORPORATE SOURCE: Basic Research Laboratory, Division of Basic Sciences, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Blood (2000), 95(12), 3939-3944
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 37
REFERENCE(S):
(1) Akagi, T; FEBS Lett 1997, V406, P263 HCAPLUS
(2) Cereseto, A; Blood 1996, V88, P1551 HCAPLUS
(3) Cesarman, E; Blood 1992, V80, P3205 HCAPLUS
(4) Chen, C; Proc Natl Acad Sci USA 1994, V91, P2684 HCAPLUS
(6) Drexler, H; Leukemia 1998, V12, P845 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21ras in PC12 cells
AB Proteolysis by the ubiquitin/proteasome pathway regulates the intracellular level of several proteins, some of which control **cell proliferation** and cell cycle progression. To det. what kinds of signaling cascades are activated or inhibited by proteasome inhibition, we treated PC12 cells with specific proteasome inhibitors and subsequently performed in-gel kinase assays. N-Acetyl-Leu-Leu-norleucinal and **lactacystin**, which inhibit the activity of the proteasome, induced the activation of p42/p44 mitogen-activated protein (MAP) kinases [extracellular signal-regulated kinases (ERKs) 1 and 2]. In contrast, N-acetyl-Leu-Leu-methional, which inhibits the activity of calpains, but not of the proteasome, failed to induce ERK activation. Uniquely, the kinetics of MAP kinase activation induced by proteasome inhibitors are very slow compared with those resulting from activation by nerve growth factor; ERK activation is detectable only after a 5-h treatment with the inhibitors, and its activity remained unchanged for at least until 27 h. **Proteasome inhibitor**-initiated ERK activation is inhibited by pretreatment with the ERK kinase inhibitor PD 98059, as well as by overexpression of a dominant-neg. form of Ras. Thus, proteasome inhibitors induce sustained ERK activation in a Ras-dependent manner. **Proteasome inhibitor**-induced neurite outgrowth, however, is not inhibited by PD 98059, indicating that sustained activation of ERKs is not the factor responsible for **proteasome inhibitor**-induced morphol. differentiation. Our data suggest the presence of a novel mechanism for activation of the MAP kinase cascade that involves proteasome activity.
ACCESSION NUMBER: 2000:5277 HCAPLUS
DOCUMENT NUMBER: 132:164025
TITLE: Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21ras in PC12 cells
AUTHOR(S): Hashimoto, Keiko; Guroff, Gordon; Katagiri, Yasuhiro
CORPORATE SOURCE: Section on Growth Factors, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: J. Neurochem. (2000), 74(1), 92-98
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41
REFERENCE(S):
(1) Alessandrini, A; Leukemia 1997, V11, P342 HCAPLUS
(2) Chen, Q; J Biol Chem 1996, V271, P18122 HCAPLUS
(3) Ciechanover, A; EMBO J 1998, V17, P7151 HCAPLUS

(4) Cowley, S; Cell 1994, V77, P841 HCAPLUS
(5) Dietrich, C; Proc Natl Acad Sci 1996, V93, P10815 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture
AB Vascular smooth muscle cells exhibit a striking plasticity and are able to change from a differentiated, contractile phenotype to a more immature, synthetic phenotype. This includes a prominent structural reorganization with loss of myofilaments and construction of a large secretory app. As a result, the cells lose their contractility and become able to migrate, proliferate, and secrete extracellular matrix components. In vivo, this phenotypic shift is a chief factor behind the involvement of smooth muscle cells in formation of atherosclerotic and restenotic lesions. Here, the effects of the proteasome inhibitors carbobenzoxy-leucyl-leucyl-leucinal, N-acetyl-leucyl-leucyl-norleucinal, and **lactacystin** on the morphol. structure and growth of rat aortic smooth muscle cells in primary culture were examd. Electron microscopic anal. revealed that the vol. d. of myofilaments was higher and the vol. d. of the endoplasmic reticulum and the Golgi complex was lower in cells exposed to these drugs than in solvent-treated controls. Moreover, diffuse material representing incompletely degraded proteins gathered in the cytoplasm of exposed cells. Similar material was also found in lysosomes. Immunogold staining showed a pos. reaction in the diffuse cytoplasmic aggregates with antibodies against ubiquitin-protein conjugates and proteasomes, whereas the material collecting in lysosomes reacted only with those against ubiquitin-protein conjugates. Moreover, weak staining for smooth muscle .alpha.-actin was noted in the cytoplasmic aggregates. Otherwise, reactivity for this protein was concd. in myofilaments. In addn. to the effects on cell structure described above, the proteasome inhibitors blocked cell multiplication. This was probably due to a decreased rate of transition into a synthetic state as well as direct interference with cell cycle progression in synthetic cells. These observations suggest that proteasomes have the major responsibility for protein degrdn. during transition of smooth muscle cells from a contractile to a synthetic phenotype. If proteasome activity is inhibited, undegraded material accumulates in the cytoplasm and is only partially taken up into lysosomes for digestion. These findings raise the possibility that proteasome inhibitors may have a beneficial effect on vascular pathologies assocd. with phenotypic modulation and proliferation of smooth muscle cells. The calpain inhibitor N-acetyl-leucyl-leucyl-methional did not affect the proliferation of vascular smooth muscle cells.
ACCESSION NUMBER: 1999:657088 HCAPLUS
DOCUMENT NUMBER: 132:146605
TITLE: Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture
AUTHOR(S): Thyberg, Johan; Blomgren, Karin
CORPORATE SOURCE: Department of Cell and Molecular Biology, Karolinska Institut, Stockholm, S-171 77, Swed.
SOURCE: Lab. Invest. (1999), 79(9), 1077-1088
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal

LANGUAGE: English
REFERENCE COUNT: 30
REFERENCE(S): (1) Hedin, U; Dev Biol 1989, V[illegible]3, P489 HCAPLUS
(2) Hedin, U; J Cell Biol 1988, V107, P307 HCAPLUS
(3) Hershko, A; Annu Rev Biochem 1998, V67, P425 HCAPLUS
(4) Huttenlocher, A; J Biol Chem 1997, V272, P32719 HCAPLUS
(5) King, R; Science 1996, V274, P1652 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening method
AB The present invention relates to compns. comprising proteasome inhibitors, such as lactocystin and analogs thereof. These compns. are used for the following purposes: (1) to disrupt mitochondrial function (useful against cancer, inflammation, adverse immune reaction and hyperthyroidism), (2) to disrupt nitric oxide synthesis (useful against inflammation and septic shock), and (3) to reverse ongoing adverse immune reactions, such as autoimmune diseases and graft rejection. In the latter case, the compns. are administered once the patient's T cells are mostly activated. Proteasome inhibitors can also be combined with immunosuppressive drugs, e.g. rapamycin, cyclosporin A, and FK506. Finally, a method for screening a compd. having a proteasome inhibition activity is also disclosed and claimed.
ACCESSION NUMBER: 1999:311103 HCAPLUS
DOCUMENT NUMBER: 130:332911
TITLE: The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening method
INVENTOR(S): Wu, Jiangping; Wang, Xin
PATENT ASSIGNEE(S): Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Can.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9922729	A1	19990514	WO 1998-CA1010	19981029
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9897318	A1	19990524	AU 1998-97318	19981029
EP 967976	A1	20000105	EP 1998-951135	19981029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: CA 1997-2219867 19971031
WO 1998-CA1010 19981029

REFERENCE COUNT: 15
REFERENCE(S): (1) Conner, E; JOURNAL OF PHARMACOLOGY AND

EXPERIMENTAL THERAPEUTICS 1997, V282(3), P1615 HCAPLUS
(2) Cui, H; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1997, V94(14), P7515 HCAPLUS
(3) Griscavage, J; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1996, V93(8), P3308 HCAPLUS
(4) Harvard College; WO 9417816 A 1994 HCAPLUS
(5) Harvard College; WO 9632105 A 1996 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 23 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI Mechanistic studies on the inactivation of the proteasome by **lactacystin** in cultured cells
AB The natural product **lactacystin** exerts its cellular antiproliferative effects through a mechanism involving acylation and inhibition of the proteasome, a cytosolic proteinase complex that is an essential component of the ubiquitin-proteasome pathway for intracellular protein degrdn. In vitro, **lactacystin** does not react with the proteasome; rather, it undergoes a spontaneous conversion (lactonization) to the active **proteasome inhibitor**, clasto-**lactacystin** .beta.-lactone. We show here that when the .beta.-lactone is added to mammalian cells in culture, it rapidly enters the cells, where it can react with the sulfhydryl of glutathione to form a thioester adduct that is both structurally and functionally analogous to **lactacystin**. We call this adduct lactathione, and like **lactacystin**, it does not react with the proteasome, but can undergo lactonization to yield back the active .beta.-lactone. We have studied the kinetics of this reaction under appropriate in vitro conditions as well as the kinetics of lactathione accumulation and proteasome inhibition in cells treated with **lactacystin** or .beta.-lactone. The results indicate that only the .beta.-lactone (not **lactacystin**) can enter cells and suggest that the formation of lactathione serves to conc. the inhibitor inside cells, providing a reservoir for prolonged release of the active .beta.-lactone.
ACCESSION NUMBER: 1997:34628 HCAPLUS
DOCUMENT NUMBER: 126:152446
TITLE: Mechanistic studies on the inactivation of the proteasome by **lactacystin** in cultured cells
AUTHOR(S): Dick, Lawrence R.; Cruikshank, Amy A.; Destree, Antonia T.; Grenier, Louis; McCormack, Teresa A.; Melandri, Francesco D.; Nunes, Sandra L.; Palombella, Vito J.; Parent, Lana A.; Plamondon, Louis; Stein, Ross L.
CORPORATE SOURCE: ProScript, Inc., Cambridge, MA, 02139, USA
SOURCE: J. Biol. Chem. (1997), 272(1), 182-188
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

L18 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2001 ACS
TI **Lactacystin**, a specific inhibitor of the proteasome, induces apoptosis in human monoblast U937 cells
AB **Lactacystin**, originally isolated from a microbe as an inducer of neuritogenesis, targets the catalytic .beta.-subunit of the proteasome, and arrests the cell cycle. Here we report for the first time that **lactacystin** induces apoptotic cell death in human monoblastic U937 cells. When U937 cells were cultured with **lactacystin**, their nuclei were shrunken, a morphol. change typical of apoptosis, and cell

viability was decreased. Electrophoretic anal. revealed that chromosomal DNAs from **lactacystin**-treated cells were cleaved in an internucleosomal ladder-like pattern, indicating that cell death occurs through an apoptotic process, which was also confirmed by DNMA fragmentation anal. using flow cytometry. These findings suggest that inhibition of the proteasome during proliferation results in apoptotic cell death, and that the proteasome is a key enzyme in the course of the cell cycle that destines the cell to proliferate, differentiate or die.

ACCESSION NUMBER: 1996:14107 HCAPLUS
DOCUMENT NUMBER: 124:75830
TITLE: **Lactacystin**, a specific inhibitor of the proteasome, induces apoptosis in human monoblast U937 cells
AUTHOR(S): Imajoh-Ohmi, Shinobu; Kawaguchi, Tomoko; Sugiyama, Shinji; Tanaka, Keiji; Omura, Satoshi; Kikuchi, Hidehiko
CORPORATE SOURCE: Inst. Medical Science, Univ. Tokyo, Tokyo, 108, Japan
SOURCE: Biochem. Biophys. Res. Commun. (1995), 217(3), 1070-7
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

L18 ANSWER 25 OF 30 CA COPYRIGHT 2001 ACS
TI p53 stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14ARF-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells
AB Human T-cell lymphotropic virus type I (HTLV-I) transforms T cells in vitro, and the viral transactivator Tax functionally impairs the tumor suppressor p53 protein, which is also stabilized in HTLV-I-infected T cells. Thus, the functional impairment of p53 is essential to maintain the viral-induced proliferation of CD4+ mature T cells. However, in the CD4+ leukemic cells of patients with adult T-cell leukemia/lymphoma (ATLL), the viral transactivator does not appear to be expressed, and p53 mutations have been found only in a fraction of patients. We sought to investigate whether p53 function is impaired, in ex vivo samples from patients with ATLL, in the absence of genetic mutations. Here we demonstrate that the p53 protein is stabilized also in ex vivo ATLL samples (10 of 10 studied) and that at least in 2 patients p53 stabilization was not assocd. with genetic mutation. Furthermore, the assessment of p53 function after ionizing radiation of ATLL cells indicated an abnormal induction of the p53-responsive genes GADD45 and p21WAF1 in 7 of 7 patients. In 2 of 2 patients, p53 regulation of cell-cycle progression appeared to be impaired as well. Because p53 is part of a regulatory loop that also involves MDM2 and p14ARF, the status of the latter proteins was also assessed in cultured or fresh ATLL cells. The p97 MDM2 protein was not detected by Western blot anal. in established HTLV-I-infected T-cell lines or ex vivo ATLL cell lysates. However, the MDM2 protein could be easily detected after treatment of cells with the specific **proteasome inhibitor lactacystin**, suggesting a normal regulation of the p53-MDM2 regulating loop. Similarly, p14ARF did not appear to be aberrantly expressed in ex vivo ATLL cells nor in any of the established HTLV-I-infected T-cell lines studied. Thus, p53 stabilization in HTLV-I infection occurs in the absence of genetic mutation and alteration of the physiol. degrdn. pathway of p53.

ACCESSION NUMBER: 133:133279 CA
TITLE: p53 stabilization and functional impairment in the absence of genetic mutation or the alteration of the p14ARF-MDM2 loop in ex vivo and cultured adult T-cell leukemia/lymphoma cells
AUTHOR(S): Takemoto, Shigeki; Trovato, Raffaella; Cereseto, Anna;

Nicot, Christophe; Kislyakova, Tatiana; Casareto, Luca; Waldmann, Thomas; Torelli, Giuseppe; Franchini, Genoveffa

CORPORATE SOURCE: Basic Research Laboratory, Division of Basic Sciences,

Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Blood (2000), 95(12), 3939-3944
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 37
REFERENCE(S): (1) Akagi, T; FEBS Lett 1997, V406, P263 CA
(2) Cereseto, A; Blood 1996, V88, P1551 CA
(3) Cesarman, E; Blood 1992, V80, P3205 CA
(4) Chen, C; Proc Natl Acad Sci USA 1994, V91, P2684 CA
(6) Drexler, H; Leukemia 1998, V12, P845 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 26 OF 30 CA COPYRIGHT 2001 ACS
TI Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21ras in PC12 cells
AB Proteolysis by the ubiquitin/proteasome pathway regulates the intracellular level of several proteins, some of which control **cell proliferation** and cell cycle progression. To det. what kinds of signaling cascades are activated or inhibited by proteasome inhibition, we treated PC12 cells with specific proteasome inhibitors and subsequently performed in-gel kinase assays. N-Acetyl-Leu-Leu-norleucinal and **lactacystin**, which inhibit the activity of the proteasome, induced the activation of p42/p44 mitogen-activated protein (MAP) kinases [extracellular signal-regulated kinases (ERKs) 1 and 2]. In contrast, N-acetyl-Leu-Leu-methional, which inhibits the activity of calpains, but not of the proteasome, failed to induce ERK activation. Uniquely, the kinetics of MAP kinase activation induced by proteasome inhibitors are very slow compared with those resulting from activation by nerve growth factor; ERK activation is detectable only after a 5-h treatment with the inhibitors, and its activity remained unchanged for at least until 27 h. **Proteasome inhibitor**-initiated ERK activation is inhibited by pretreatment with the ERK kinase inhibitor PD 98059, as well as by overexpression of a dominant-neg. form of Ras. Thus, proteasome inhibitors induce sustained ERK activation in a Ras-dependent manner. **Proteasome inhibitor**-induced neurite outgrowth, however, is not inhibited by PD 98059, indicating that sustained activation of ERKs is not the factor responsible for **proteasome inhibitor**-induced morphol. differentiation. Our data suggest the presence of a novel mechanism for activation of the MAP kinase cascade that involves proteasome activity.

ACCESSION NUMBER: 132:164025 CA
TITLE: Delayed and sustained activation of p42/p44 mitogen-activated protein kinase induced by proteasome inhibitors through p21ras in PC12 cells
AUTHOR(S): Hashimoto, Keiko; Guroff, Gordon; Katagiri, Yasuhiro
CORPORATE SOURCE: Section on Growth Factors, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: J. Neurochem. (2000), 74(1), 92-98
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41
REFERENCE(S):
(1) Alessandrini, A; Leukemia 1997, V11, P342 CA
(2) Chen, Q; J Biol Chem 1996, V271, P18122 CA
(3) Ciechanover, A; EMBO J 1998, V17, P7151 CA
(4) Cowley, S; Cell 1994, V77, P841 CA
(5) Dietrich, C; Proc Natl Acad Sci 1996, V93, P10815 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 27 OF 30 CA COPYRIGHT 2001 ACS
TI Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture
AB Vascular smooth muscle cells exhibit a striking plasticity and are able to change from a differentiated, contractile phenotype to a more immature, synthetic phenotype. This includes a prominent structural reorganization with loss of myofilaments and construction of a large secretory app. As a result, the cells lose their contractility and become able to migrate, proliferate, and secrete extracellular matrix components. In vivo, this phenotypic shift is a chief factor behind the involvement of smooth muscle cells in formation of atherosclerotic and restenotic lesions. Here, the effects of the proteasome inhibitors carbobenzoxy-leucyl-leucyl-leucinal, N-acetyl-leucyl-leucyl-norleucinal, and **lactacystin** on the morphol. structure and growth of rat aortic smooth muscle cells in primary culture were examd. Electron microscopic anal. revealed that the vol. d. of myofilaments was higher and the vol. d. of the endoplasmic reticulum and the Golgi complex was lower in cells exposed to these drugs than in solvent-treated controls. Moreover, diffuse material representing incompletely degraded proteins gathered in the cytoplasm of exposed cells. Similar material was also found in lysosomes. Immunogold staining showed a pos. reaction in the diffuse cytoplasmic aggregates with antibodies against ubiquitin-protein conjugates and proteasomes, whereas the material collecting in lysosomes reacted only with those against ubiquitin-protein conjugates. Moreover, weak staining for smooth muscle .alpha.-actin was noted in the cytoplasmic aggregates. Otherwise, reactivity for this protein was concd. in myofilaments. In addn. to the effects on cell structure described above, the proteasome inhibitors blocked cell multiplication. This was probably due to a decreased rate of transition into a synthetic state as well as direct interference with cell cycle progression in synthetic cells. These observations suggest that proteasomes have the major responsibility for protein degrdn. during transition of smooth muscle cells from a contractile to a synthetic phenotype. If proteasome activity is inhibited, undegraded material accumulates in the cytoplasm and is only partially taken up into lysosomes for digestion. These findings raise the possibility that proteasome inhibitors may have a beneficial effect on vascular pathologies assocd. with phenotypic modulation and proliferation of smooth muscle cells. The calpain inhibitor N-acetyl-leucyl-leucyl-methional did not affect the proliferation of vascular smooth muscle cells.
ACCESSION NUMBER: 132:146605 CA
TITLE: Effects of proteasome and calpain inhibitors on the structural reorganization and proliferation of vascular smooth muscle cells in primary culture
AUTHOR(S): Thyberg, Johan; Blomgren, Karin

CORPORATE SOURCE: Department of Cell and Molecular Biology, Karolinska Institut, Stockholm, S-171 77, Swed.
SOURCE: Lab. Invest. (1999), 79(9), 10[redacted]1088
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30
REFERENCE(S): (1) Hedin, U; Dev Biol 1989, V133, P489 CA
(2) Hedin, U; J Cell Biol 1988, V107, P307 CA
(3) Hershko, A; Annu Rev Biochem 1998, V67, P425 CA
(4) Huttenlocher, A; J Biol Chem 1997, V272, P32719 CA
(5) King, R; Science 1996, V274, P1652 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 28 OF 30 CA COPYRIGHT 2001 ACS
TI The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening method
AB The present invention relates to compns. comprising proteasome inhibitors, such as lactocystin and analogs thereof. These compns. are used for the following purposes: (1) to disrupt mitochondrial function (useful against cancer, inflammation, adverse immune reaction and hyperthyroidism), (2) to disrupt nitric oxide synthesis (useful against inflammation and septic shock), and (3) to reverse ongoing adverse immune reactions, such as autoimmune diseases and graft rejection. In the latter case, the compns. are administered once the patient's T cells are mostly activated. Proteasome inhibitors can also be combined with immunosuppressive drugs, e.g. rapamycin, cyclosporin A, and FK506. Finally, a method for screening a compd. having a proteasome inhibition activity is also disclosed and claimed.
ACCESSION NUMBER: 130:332911 CA
TITLE: The use of proteasome inhibitors for treating cancer, inflammation, autoimmune disease, graft rejection and septic shock, and screening method
INVENTOR(S): Wu, Jiangping; Wang, Xin
PATENT ASSIGNEE(S): Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Can.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9922729	A1	19990514	WO 1998-CA1010	19981029
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9897318	A1	19990524	AU 1998-97318	19981029
EP 967976	A1	20000105	EP 1998-951135	19981029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: CA 1997-2219867 19971031
WO 1998-CA1010 19981029

REFERENCE COUNT: 15
REFERENCE(S): (1) Conner, E; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1997, V282(3), P1615 CA
(2) Cui, H; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1997, V94(14), P7515 CA
(3) Griscavage, J; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1996, V93(8), P3308 CA
(4) Harvard College; WO 9417816 A 1994 CA
(5) Harvard College; WO 9632105 A 1996 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 29 OF 30 CA COPYRIGHT 2001 ACS
TI Mechanistic studies on the inactivation of the proteasome by **lactacystin** in cultured cells
AB The natural product **lactacystin** exerts its cellular antiproliferative effects through a mechanism involving acylation and inhibition of the proteasome, a cytosolic proteinase complex that is an essential component of the ubiquitin-proteasome pathway for intracellular protein degrdn. In vitro, **lactacystin** does not react with the proteasome; rather, it undergoes a spontaneous conversion (lactonization) to the active **proteasome inhibitor**, clasto-**lactacystin** .beta.-lactone. We show here that when the .beta.-lactone is added to mammalian cells in culture, it rapidly enters the cells, where it can react with the sulfhydryl of glutathione to form a thioester adduct that is both structurally and functionally analogous to **lactacystin**. We call this adduct lactathione, and like **lactacystin**, it does not react with the proteasome, but can undergo lactonization to yield back the active .beta.-lactone. We have studied the kinetics of this reaction under appropriate in vitro conditions as well as the kinetics of lactathione accumulation and proteasome inhibition in cells treated with **lactacystin** or .beta.-lactone. The results indicate that only the .beta.-lactone (not **lactacystin**) can enter cells and suggest that the formation of lactathione serves to conc. the inhibitor inside cells, providing a reservoir for prolonged release of the active .beta.-lactone.
ACCESSION NUMBER: 126:152446 CA
TITLE: Mechanistic studies on the inactivation of the proteasome by **lactacystin** in cultured cells
AUTHOR(S): Dick, Lawrence R.; Cruikshank, Amy A.; Destree, Antonia T.; Grenier, Louis; McCormack, Teresa A.; Melandri, Francesco D.; Nunes, Sandra L.; Palombella, Vito J.; Parent, Lana A.; Plamondon, Louis; Stein, Ross L.
CORPORATE SOURCE: ProScript, Inc., Cambridge, MA, 02139, USA
SOURCE: J. Biol. Chem. (1997), 272(1), 182-188
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

L18 ANSWER 30 OF 30 CA COPYRIGHT 2001 ACS
TI **Lactacystin**, a specific inhibitor of the proteasome, induces apoptosis in human monoblast U937 cells
AB **Lactacystin**, originally isolated from a microbe as an inducer of neuritogenesis, targets the catalytic .beta.-subunit of the proteasome, and arrests the cell cycle. Here we report for the first time that **lactacystin** induces apoptotic cell death in human monoblastic U937

cells. When U937 cells were cultured with **lactacystin**, their nuclei were shrunken, a morphol. change typical of apoptosis, and cell viability was decreased. Electrophoretic anal. revealed that chromosomal DNAs from **lactacystin**-treated cells were cleaved in an internucleosomal ladder-like pattern, indicating that cell death occurs through an apoptotic process, which was also confirmed by DNMA fragmentation anal. using flow cytometry. These findings suggest that inhibition of the proteasome during proliferation results in apoptotic cell death, and that the proteasome is a key enzyme in the course of the cell cycle that destines the cell to proliferate, differentiate or die.

ACCESSION NUMBER: 124:75830 CA
TITLE: **Lactacystin**, a specific inhibitor of the proteasome, induces apoptosis in human monoblast U937 cells
AUTHOR(S): Imajoh-Ohmi, Shinobu; Kawaguchi, Tomoko; Sugiyama, Shinji; Tanaka, Keiji; Omura, Satoshi; Kikuchi, Hidehiko
CORPORATE SOURCE: Inst. Medical Science, Univ. Tokyo, Tokyo, 108, Japan
SOURCE: Biochem. Biophys. Res. Commun. (1995), 217(3), 1070-7
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English